



The GMP Questions & Answers Guide

- GMP Advisor -

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About this document

Searching for concrete answers to GMP questions is a time-consuming activity.
This document is intended to provide a single source of information.

We have summarized GMP questions and answers from Regulators around the world.

In addition to EMA, FDA, Health Canada, MHRA (UK), and ICH we have also used Q&As from the ECA Foundation. The subject index contains some of the “GMP Key Words” and allows to find Q&As addressing the relevant topic.

It is the intension to update this comprehensive collection and to also add new Q&As once they are available.



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While every effort has been made to assure the accuracy of the contents of this brochure, ECA Academy cannot be held liable for any errors or omissions.

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1. EMA Europe

1.1. General GMP Requirements

EU GMP guide part I: Basic requirements for medicinal products: Chapter 1: Pharmaceutical quality system (New July 2018)

1. What should be the frequency of the product quality review (PQR)?

The product review is expected annually. Review timeframes can be appropriately adjusted based upon manufacturing and campaign duration with adequate justification. The timeframe criteria should be established in a SOP. The trending can include results gathered from the previous period to ensure its robustness. Even if no manufacturing has occurred in the review period, the quality and regulatory review should be conducted as per section 1.10 and include stability results, returns, complaints, recalls, deviations (including those arising from qualification and validation activities) and regulatory background. The review of the last PQR should also be conducted.

EU GMP guide part I: Basic requirements for medicinal products: Chapter 3: Equipment

1. Should metal detectors be used routinely in manufacturing processes for certain dosage forms e.g. tablet compression and encapsulation processes? H+V February 2015

Metal could originate from raw materials as well as from equipment in manufacturing processes where metal parts could generate fragments due to the conditions of operation or damage to the equipment. It is recommended that metal detection is used for processes prone to this.

In order to avoid routine use of metal detectors the company must demonstrate that it has identified and managed the risks such that the use of metal detectors for that particular process is not needed.

EU GMP guide part I: Basic requirements for medicinal products: Chapter 3: Shared manufacturing facilities

Questions and answers on implementation of risk-based prevention of cross contamination in production.

Q1. Are Health-Based Exposure Limits (HBELs) required for all medicinal products?

A: Yes, HBELs should be established for all medicinal products.

The toxicological or pharmacological data, on which the HBEL calculation relies, requires periodical re-assessment throughout a product's lifecycle.

Q2. Is there a framework that could be used to define the significance of the Health-Based Exposure Limit (HBEL) such that there can be broad guidance on the extent of Quality Risk Management (QRM) and control measures required?

A: Firstly, it should be recognised that hazard varies on a continuum scale and that there are no firm cut off points, risk should be controlled on a proportionate basis. However, as a broad hypothetical model the following figure could be considered to show the increasing level of hazard (red being highest hazard) presented by products and there should be a commensurate increase in the level of control to prevent potential cross contamination in a shared facility. Actual HBEL values should be used in QRM studies to determine the actual controls required.

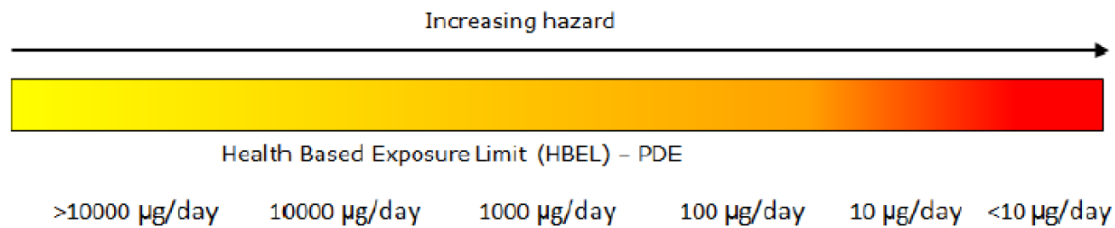


Diagram developed from an original concept published by ISPE. Source: ISPE Baseline® Pharmaceutical Engineering Guide, Volume 7 – Risk-Based Manufacture of Pharmaceutical Products, International Society for Pharmaceutical Engineering (ISPE), Second Edition, July 2017.

Q3. How should manufacturers use the HBELs?

A: The role of HBELs in determining cleaning limits is explained in Q&A 6. However, the purpose of generating HBELs goes beyond justification of cleaning limits. Once the health-based assessment has been completed and the HBEL confirmed, these data should be used via a Quality Risk Management process to determine what controls need to be put in place and to assess if existing organisational and technical control measures are adequate or if they need to be supplemented. This Quality Risk Management process should be carried out prospectively in the case of new equipment/facility to determine what control measures are required.

It is expected that for products which present a higher potential harm to patients/animals, more elaborate organisational and technical control measures will be required. Using a structured Quality Risk Management process, manufacturers should consider the risks of cross contamination down to the established level from the HBEL. During the QRM study manufacturers should consider how easily such a quantity of contamination could occur, without detection, at batch and unit dose level. The level of detail in the QRM process should be commensurate with the potential harm as indicated by the HBEL and the suitability of control measures supported by practical and science-based evidence.

Manufacturers should be mindful that cross contamination controls implemented previously may not adequately assure control of the cross contamination risk in the context of the HBEL approach. Additional observation of working practices, investigation and analysis may be required to provide full practical confidence in the effectiveness of controls.

Where control measures cannot adequately assure that the potential contamination is consistently controlled to a level below that of the HBEL then the products concerned should be manufactured in dedicated facilities.

Q4. What competencies are required for the person developing the Health-Based Exposure Limits (HBEL)?

A: Health-Based Exposure Limits should be determined by a person who has adequate expertise and experience in toxicology/pharmacology, familiarity with pharmaceuticals as well as experience in the determination of health-based exposure limits such as Occupational Exposure Levels (OEL) or Permitted Daily Exposure (PDE).

Where experts are contracted to provide the HBEL, contractual agreements in compliance with Chapter 7 requirements should be in place prior to work being conducted. It is not considered acceptable for manufacturers to 'purchase' HBEL assessments without recording an assessment of the suitability of the provider (including the specific technical expert) as a qualified contractor.

Q5. What responsibility do contract givers have to contract manufacturers in relation to data to support a HBEL assessment?

A: Contract givers should either provide a full HBEL assessment to contract manufacturers or provide the data to allow the contract manufacturer to conduct the HBEL assessment. In either case the HBEL assessment, including data references and relevant experts should be available on request during inspection of the manufacturer.

Q6. How can limits for cleaning purposes be established?

A: Although the EMA guideline (EMA/CHMP/CVMP/SWP/169430/2012) may be used to justify cleaning limits (as per Introduction paragraph 3), it is not intended to be used to set cleaning limits at the level of the calculated HBEL.

For existing products, manufacturer's historically used cleaning limits should be retained and can be considered alert limits provided that when taking cleaning process capability into account, they provide sufficient assurance that excursions above the HBEL will be prevented. A similar process should be adopted when establishing cleaning alert levels for products introduced into a facility for the first-time.

Results above the alert cleaning limit should trigger an investigation and, where appropriate, corrective action to bring the cleaning process performance within the alert cleaning limits. Repeated excursions above the alert cleaning limit will not be considered acceptable where these indicate that the cleaning method is not in control. Recognised appropriate statistical methods may be used to determine whether the cleaning process is in control or not.

Q7. Is analytical testing required at product changeover, on equipment in shared facilities, following completion of cleaning validation?

A: Analytical testing is expected at each changeover unless justified otherwise via a robust, documented Quality Risk Management (QRM) process. The QRM process should consider, at a minimum, each of the following:

- the repeatability of the cleaning process (*manual cleaning is generally less repeatable than automated cleaning*);
- the hazard posed by the product;
- whether visual inspection can be relied upon to determine the cleanliness of the equipment at the residue limit justified by the HBEL.

Q8. What are the requirements for conducting visual inspection as per Q&A 7?

A. When applying visual inspection to determine cleanliness of equipment, manufacturers should establish the threshold at which the product is readily visible as a residue. This should also take into account the ability to visually inspect the equipment, for example, under the lighting conditions and distances observed in the field.

Visual inspection should include all product contact surfaces where contamination may be held, including those that require dismantling of equipment to gain access for inspection and/or by use of tools (for example mirror, light source, boroscope) to access areas not otherwise visible. Non-product contact surfaces that may retain product that could be dislodged or transferred into future batches should be included in the visual inspection.

Written instructions specifying all areas requiring visual inspection should be in place and records should clearly confirm that all inspections are completed.

Operators performing visual inspection require specific training in the process including periodic eye sight testing. Their competency should be proven through a practical assessment.

Q9. Is it acceptable to simply segregate products of a common therapeutic classification in a dedicated area as a means of controlling risk of cross contamination?

A: Manufacturers cannot just segregate common products from other product types as a means of dealing with the risk to patient and animal safety. Although this may prevent contamination of other product classes it does not address the possibility for cross contamination within product classes. The approach taken to control cross contamination between individual products within a class produced in the same dedicated area should follow the principles in Q&A 3. This should include implementation of appropriate organisational and technical control measures to prevent contamination between such products within product specific HBELs.

Q10. Is the use of LD50 to determine Health-Based Exposure Limits for drug products acceptable?

A: No, LD50 is not an adequate point of departure to determine a HBEL for drug products.

Q11. Can Ectoparasiticides be manufactured or primary packed in common equipment with other categories of medicinal products for human or veterinary use?

A: If a HBEL cannot be determined or data cannot support manufacture in shared facilities then the Ectoparasiticides should be manufactured in dedicated facilities.

Q12. What needs to be taken into account when manufacturing Veterinary Medicinal Products for different species in the same facility?

A: The guideline on setting health-based exposure limits indicates that the carry over limit should generally be derived using the human HBEL.

However, in cases where there is concern relating to known susceptibility of a particular species (e.g. monensin in horses) the HBEL approach should take into account knowledge of specific animal toxicity when evaluating products manufactured in shared facilities/equipment.

Q13. Should the HBEL be re-assessed throughout the phases of development of Investigational Medicinal Products (IMPs)?

A: Health-Based Exposure Limits should be established based on all available data, and particularly as the knowledge base for IMPs is continually evolving the basis for establishing the HBEL, should be regularly reviewed taking account of any new relevant data.

**EU GMP guide part I: Basic requirements for medicinal products:
Chapter 5: Production**1. Is an audit performed by a third party acceptable? H+V July 2006

The document 'guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of [active substances](#) used as starting materials', published as part of the [Community procedures](#), states that it is expected that manufacturing authorisation holders will gain assurance that the [active substances](#) they use are manufactured in accordance with GMP through audit of the active-substance suppliers. Small manufacturers may not have the necessary expertise or resource to conduct their own audits.

Section 5.25 of the [GMP guideline](#) requires starting materials to be purchased from approved suppliers and about whom the manufacturer has a particular and thorough knowledge.

An audit conducted by the manufacturing authorisation holder itself should be integral to the manufacturer's quality assurance system and subject to the basic GMP requirements, i.e. conducted by properly qualified and trained staff, in accordance with approved procedures. It should be properly documented. These aspects can be inspected as necessary by the competent authorities.

If a third party is involved, the arrangements should be subject to chapter 7 of the [GMP guideline](#).

There should be evidence that the contract-giver has evaluated the contract-acceptor with respect to the aspects described above.

All parties involved should be aware that audit reports and other documentation relating to the audit will be made available for inspection by the competent authorities if requested. This should normally provide sufficient assurance that the results of an audit carried by the third party are credible, thus waiving the need for an audit conducted by the manufacturing authorisation holder itself. However, it must also be satisfactorily demonstrated that there are no conflicts of interests. Conflicts of interests could arise for example from:

- a commercial relationship between the organisation performing the audit and the organisation being audited;
- a personal conflict on the part of the auditor where he / she has been employed by the organisation being audited in the recent past (i.e. within the last three years) or has a financial interest in it.

This topic should also be addressed in the technical contractual arrangements. Any measures taken by the contract-giver should be documented, e.g. signed undertakings by the auditors.

Similarly, the principles outlined above could be used to allow sharing of audit reports between different manufacturing-authorisation holders using the same [active substance](#) supplier, provided that the scope of the audits can be shown to be applicable to the [active substances](#) of mutual interest.

2. Is it possible to use multiple batch numbers in packaging of medical products? H+V January 2005

GMP inspectors have discussed the desirability of more than one batch number appearing on the packaging of [medicinal products](#).

It is normal practice for companies to use a bulk batch number that is different from the finished product batch when the bulk is packaged as several sub-batches. There is normally an element in the numbering format common to the bulk batch and finished product batches that clearly ties these together. The difference normally takes the form of a suffix, prefix or both.

A matter of concern for the inspectors is when the bulk and finished product batch numbers are completely different and there is no obvious connection between the two. Even though the

manufacturer has a system of traceability, the inspectors agree that this is an undesirable practice and should be avoided. The main reasons for this are:

- patients and healthcare professionals may mistakenly believe that there has been a packaging error;
- hospitals often remove products from the outer packaging and traceability may therefore be lost;
- confusion may occur in the case of recall, rendering such action potentially ineffective.

It is accepted that there may be exceptional cases where multiple batch numbers are displayed on a pack, such as in combination product packages. In addition, products that require relabelling following [parallel distribution](#) are expected to display the original manufacturer's batch number. Manufacturers are recommended to discuss individual cases with the relevant supervisory authority. In all cases, traceability must be maintained.

3. What are the expectations with regard to documentation and verification of the supply chain for active substances (ref. Paragraph 5.29, Chapter 5 EU GMP Guide)? H+V August 2015

The supply chain for each [active substance](#) must be established back to the manufacture of the [active substance](#) starting materials. This should be documented and must be kept current. The risks associated with this supply chain should be formally documented. Control of each incoming consignment of [active substance](#) should include verification that it has been received from the approved supplier and approved manufacturer. The entire supply chain should be verified for a supplied batch periodically to establish a documented trail for the batch back to the manufacturer(s) of the [active substance](#) starting materials. The frequency of this verification should be based on risk.

4. Is it acceptable to pack (primary and/or secondary packaging) multiple batches of the same product (e.g. tablets, capsules, lozenges) in order to obtain a single batch as a "super batch"? H+V July 2018

Normally, such an approach should be avoided as each batch is made from the same initial quantity of material and should remain as an individual batch of finished [medicinal product](#) bearing a unique batch number. Therefore, any other approach should be thoroughly justified by applying the principles of Quality Risk Management (QRM) taking into account at least the following criteria:

- length of time the equipment has been in use;
- [pharmaceutical form](#) of the drug product that cannot be homogenised (tablet, capsules, etc);
- expiry date of the drug products;
- ongoing stability study design and results;
- reference samples plan for each batch;
- criticality of the drug product and the risk of shortage that may arise from any quality issue;
- prior approval of the MAH.

Irrespective of the outcome of the QRM, such an approach can only be accepted if each individual batch of the combined "super batch" undergoes all the in-process control and finished drug product testing as specified in the [marketing authorisation](#) dossier.

In the event of a recall, the entire "super batch" should be recalled.

EU GMP guide part I: Basic requirements for medicinal products: Chapter 8: Complaints, Quality Defects and Product Recalls

1. What are the quality defect reporting requirements of EU GMP?

Suspected product quality defects (e.g. product deterioration, packaging mix-up, among others) should be reported to the [competent authority](#) with responsibility for the manufacturing site (or importer where the manufacturer is located outside the EEA), and to the [competent authority](#) in each EEA market supplied. In case of impact to EU [centrally authorised products](#), the EMA must also be notified. This notification should be prior to taking any market action, unless, as per paragraph 8.26 of Chapter 8, the need for market action is so serious as to warrant immediate action to protect patient or animal health.

Confirmation of a quality defect does not require completion of the investigation. Reporting should be initiated when available information supports the detection of the issue and when the initial assessment of the potential risks presented to patients/animals indicates that it could result in market action. Notification to competent authorities should typically take place within one working day of confirmation that reporting is required.

In cases where a suspected quality defect involves multiple manufacturing sites, reporting responsibilities should be defined in a technical agreement. It is normal expectation that the MAH and site of final EU batch certification should take the lead on reporting, unless otherwise justified. Manufacturers are encouraged to notify their [national competent authority](#) (or EU Supervisory Authority for sites located outside the EEA) of confirmed serious GMP issues with the potential to lead to a suspected product defect requiring market action (e.g. media fill failure, serious equipment failure, etc.). Confirmation of a serious GMP issue does not require completion of the investigation; reporting should be initiated when available information confirms the detection of the issue. Serious GMP issues which may result in an abnormal restriction in supply should be notified to the MAH and relevant competent authorities in accordance with legal obligations given in Art 23(2) of Directive 2001/83/EC, Art 27 of Directive 2001/82/EC, Regulation 726/2004 and EMA guidance¹: In the event that a [medicinal product](#) which is the subject of a [marketing authorisation](#) issued by an EEA authority, and which is marketed in another [third country](#) (or countries) then *the [marketing authorisation holder](#) shall forthwith inform the relevant EU [competent authority](#) of any prohibition or restriction imposed by the competent authorities of any country in which the [medicinal product](#) is marketed and of any other new information which might influence the evaluation of the benefits and risks of the [medicinal product](#) concerned* (e.g. recalls or serious GMP issues). This is even if the particular batch subject to the prohibition or restriction is not marketed in the EEA. In cases where national competent authorities set additional national expectations regarding what quality defects should be reported and the timelines for reporting, these should be complied with.

¹http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000238.jsp&mid=WC0b01ac0580024593

2. For the purposes of product recall, at what stage in the supply chain is a product considered to be 'placed on the market' (ref: Chapter 8 paragraph 8.21)?

A batch recall is defined in the Compilation of Community Procedures as "The action of withdrawing a batch from the distribution chain and users. A batch recall may be partial, in that the batch is only withdrawn from selected distributors or users". This definition covers the entire distribution chain from all points following manufacture through to the end user, the patient. Also, it is possible that the MAH or its subsidiaries are actors in the supply chain, acting as the distributor in certain cases. In such cases, the MAH or its subsidiaries should be regarded as also being part of the distribution chain. A batch of [medicinal product](#) is considered to have been 'placed on the market' when one of the following takes place:

- A batch has been Qualified Person (QP) certified and has been made available for sale on the stock management system of the pre-wholesaler/primary wholesaler, etc.
- A batch has been QP certified and supplied to a facility where the manufacturer has no further control over when the product is transferred to saleable stock. This applies even if within the pre-wholesaler/primary wholesaler network.
- In the case of supply chain models where the manufacturer or primary wholesaler supplies direct to the customer (e.g. pharmacy), the batch has been placed on the market from the time of the first customer supply of product from the batch.

National competent authorities should be notified of all recall action proposed after the product has been placed on the market. In situations where the MAH can demonstrate that the batch is reconciled without issuing a recall notice, the [national competent authority](#) may agree that public recall communication throughout the distribution network is not necessary.

It is acknowledged that certain short expiry products (e.g. radiopharmaceuticals, [advanced therapy medicinal products](#), etc.) may be shipped under quarantine prior to certification. Retrieval of batches during this quarantine period may be managed within the pharmaceutical quality system.

1.2. EU GMP guide part II: Basic requirements for active substances used as starting materials: GMP compliance for active substances

1. How can GMP compliance for active-substance manufacturers be demonstrated? H+V April 2011 Directive 2001/83/EC as amended (Directive 2001/82/EC for veterinary [medicinal products](#)) states that manufacturing-authorisation holders are obliged to use, as starting materials, only [active substances](#) that have been manufactured in accordance with the detailed [guidelines](#) on GMP for starting materials. Thus the legislation puts the responsibility on the manufacturing-authorisation holders using

the [active substance](#) and does not foresee mandatory routine inspections of active-substance manufacturers.

To provide guidance on how GMP compliance of active-substance manufacturers should be established, guidance documents have been published on this website, including the 'guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of [active substances](#) used as starting materials' as part of the [Community procedures](#). This document states that it is expected that manufacturing authorisation holders will normally gain assurance that the [active substances](#) it uses are manufactured in accordance with GMP through audit of the active-substance suppliers.

In addition, a number of questions and answers on audits of active-substance manufacturers on this page provide further guidance.

2. Do I need to perform an audit of an active substance supplier if it has been inspected by an inspectorate from a European Economic Area (EEA) Member State and a valid GMP certificate is available? H+V July 2006

Manufacturing-authorisation holders sometimes confuse the role of inspectorates with their own obligations but nevertheless, when inspection reports or GMP certificates issued by European Economic Area (EEA) mutual-recognition-agreement (MRA) partners or other recognised authorities are available, these can provide useful information to manufacturing authorisation holders. However, these alone cannot fulfil the statutory obligations of the manufacturing authorisation holder or the requirements of section 5.29 of the [GMP guideline](#), but the results of inspections may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit programme of active-substance suppliers.

3. Is it acceptable to perform a remote assessment based on, for example, questionnaires, review of documents, ISO 9000 certification, results of analytical testing and historical experience with the supplier? H+V July 2016

The EEA inspectorates are not generally in favour of 'paper-based audits' *per se* as they do not provide the same level of assurance as on-site assessments, but do accept that they have a part to play in a risk-based strategy.

They may be particularly applicable when recent positive inspection information is available and where satisfactory audits have been concluded in the past. They cannot replace on-site audits of active-substance suppliers but can be a useful interim and temporary measure within the manufacturer's audit programme.

4. How do the new requirements affect importers of medicinal products? H+V July 2006

Importers are manufacturing-authorisation holders and so the obligations under Article 46f/50f of [Directive 2001/83\(2\)](#) apply to them. For importers, the possibility of a second-party audit performed by the third-country manufacturer that uses the [active substance](#) as a starting material may be a further option.

Importers are already obliged to ensure that the third-country manufacturer complies with standards of GMP equivalent to those of the European Community and should have established arrangements in line with chapter 7 of the [GMP guideline](#). They should therefore be fully satisfied that the third-country manufacturer has adequately demonstrated that the [active substances](#) it uses for products destined for the European Community have been manufactured in accordance with GMP.

Importers may of course choose to verify the standards of GMP at the active-substance suppliers themselves or through a third party. Whichever option is chosen, the questions and answers above are also relevant.

5. Is it possible to ask for a voluntary inspection of an active substance manufacturer? H+V February 2015

First, the responsibility for only using [active substances](#) that have been manufactured in accordance with GMPs is placed on the holders of a manufacturing authorisation (MA). An inspection of the [active substance](#) manufacturer by an EEA authority does not liberate a MA holder from this responsibility. Article 111 (1f) of [Directive 2001/83/EC](#) and Article 80(1) of [Directive 2001/82/EC](#), have provision for the [competent authority](#) of the Member State concerned to carry out inspections of starting material manufacturers at the specific request of the manufacturer. The request for the inspection should be made to the EEA [competent authority](#) where the site is located or, in case of sites located in third countries, to a [competent authority](#) where the starting material is used in the manufacture of [medicinal products](#). If this is not the case, any EEA authority can be approached.

There is no guarantee that such a request will be fulfilled since competent authorities primarily use risk-based principles to plan starting material inspections. Thus, when a starting material manufacturer applies for a voluntary inspection, this does not constitute an obligation for the [competent authority](#) to trigger an inspection.

6. The notice to applicants requires the submission of a declaration signed by the qualified person (QP) that the active substance used is manufactured in accordance with GMP. ... H+V Sept 2008

The notice to applicants requires the submission of a declaration signed by the qualified person (QP) that the [active substance](#) used is manufactured in accordance with GMP. The [active substance](#) in my product is widely used, but not normally as a pharmaceutical [active substance](#), and I am having some difficulty in confirming compliance.

What should I do to furnish the required declaration? H+V September 2008

Full compliance with GMP for finished products and [active substances](#) is a legal obligation for manufacturing authorisation holders. It is recognised that for a small number of [medicinal products](#), the primary use of the [active substance](#) is not in a [medicinal product](#) and the producer may therefore not be aiming to meet the specific requirements of pharmaceutical customers that represent an insignificant volume of business.

Alternative sources should normally be sought, but in exceptional cases the manufacturing authorisation holder should assess and document to which extent GMP is complied with and provide a risk-based justification for the acceptance of any derogation.

The declaration provided by the QP should set out in detail the basis for declaring that the standards applied provide the same level of assurance as GMP. The European Medicines Agency will collect experience with this approach, which can be used as a basis for discussion on related amendments to [guidelines](#) in the future.

7. What kind of GMP documentation is needed for an active substance manufacturer that performs sterilization of an active substance? July 2010

Update January 2019: This Q&A has been superseded by the [Guideline](#) on the sterilisation of the [medicinal product](#), [active substance](#), [excipient](#) and primary container. Please refer to this [guideline](#) for further information.

The GMP basic requirements for [active substances](#) used as starting materials (EU [GMP guideline](#) part II) only applies to the manufacture of sterile [active substances](#) up to the point immediately prior to the [active substance](#) being rendered sterile. The sterilisation and aseptic processing of sterile [active substances](#) are not covered by this [guideline](#) and should be performed in accordance with GMP for [medicinal products](#) (Commission Directive 2003/94/EC as interpreted in the basic requirements for [medicinal products](#) including annex 1 of the EU [GMP guideline](#) part I). This implies that for any active-substance manufacturer that performs sterilisation and subsequent aseptic handling of the [active substance](#), a valid manufacturing authorisation or GMP certificate from an EEA authority or from an authority of countries where MRA or other Community arrangements apply has to be submitted. The active-substance manufacturer also has to submit data on the sterilisation process of the [active substance](#) (including validation data) to the marketing authorisation applicant or holder for inclusion in the dossier submitted for the finished product and approval by the licensing authorities.

8. During inspections, why do inspectors sometimes ask to see reports of audits of active substance manufacturers carried out by the medicinal product manufacturer? H+V May 2013

Inspectors may need to see audit reports during inspections as part of the assessment of the manufacturing authorisation holder's systems for confirming GMP compliance of [active substance](#) manufacturers or suppliers. Inspectors will expect to see the full details of these reports upon request, including responses received from the audited site, [indication](#) of closure of deficiencies raised or commitments made.

9. What expectations do inspectors have for the content of reports of audits of active substance manufacturers carried out by the medicinal-product manufacturer? H+V May 2013

As a minimum, the following is expected to be included in the report:

- The full postal address of the site. The auditors must be identified by full name and their employer recorded. If the audit is conducted on behalf of other parties this should be clear in the report. Where an audit report is obtained through a third party, the manufacturing authorisation holder is responsible for ensuring the validity and impartiality of the audit report.

The identity of key staff participating in the audit should be recorded along with their roles. The full contact details of the person through which the audit was arranged should be recorded including contact details (e-mail address, telephone number). The dates of the audit should be recorded, with the full-day equivalents clarified if full days were not spent on site. A justification should be recorded for the duration of the audit. If, in [exceptional circumstances](#), the audit had to be restricted to fewer days on site than required by the scope of the audit, the reasons should be explained and the conclusions with respect to the GMP status of the site should be justified. Background information on the [active substance](#) manufacturer should be recorded; this should include the company ownership, the age of the site, the number of staff employed in total and for the specific products being audited. The role of the site in manufacture of the [active substances](#) being audited should also be clarified for each of the [active substances](#) being audited, e.g. if the site performs the full manufacture or only part of the manufacture.

- The scope of the audit should be clearly stated e.g. what activities (against European Union GMP part II / International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ([ICH](#)) Q7 chapters) were covered. The activities which were not covered by the audit should also be clearly recorded. Auditors should identify the high risk areas for audit specific to the site or products being audited. For example, these could include but not be limited to:
 - process, cleaning or validation;
 - risk of cross contamination with other [active substances](#) or other substances;
 - potential for generation of unknown impurities;
 - risk of mix-up of materials and products through materials handling or packing;
 - change control;
 - deviation recording or management;
 - security sealing of [active substance](#) containers and security or temperature control of shipments.
- Subsequent audits conducted as part of the ongoing supplier audit program may have a reduced scope focusing on the highest risk areas. In such cases the highest risk areas should be identified and justified.
- A list should be recorded of all [active substances](#) directly included in the audit scope plus other [active substances](#) or intermediates (or other products) manufactured at the site.

There should be a clear record of the products, the stages of manufacture and the buildings audited. If access was denied to any relevant areas of the site this should be recorded and explained. The list should clarify which of the [active substances](#) in the scope of the audit are manufactured in multi-purpose equipment or buildings as either final product or any of the intermediate stages.

- Dates of any previous audit conducted by or on behalf of the same manufacturing- authorisation holder should be recorded. If any of the audits did not conclude with a positive GMP compliance status, a brief summary of the reasons for this should be recorded.
- Each of the applicable sections of EU GMP part II should form sections of the report with a summary of what was examined, the key findings and compliance with the requirements of each section. The report should clearly state findings against each activity audited with particular focus on the high risk areas. Any GMP deficiency identified during the audit must be clearly recorded with its criticality defined. An explanation should be given, in the report or in a supporting standard operating procedure, of the categorisation system used to classify deficiencies, e.g. critical, major or minor.
- Responses to the audit by the active-substance manufacturer should be reviewed by the auditors. Corrective and preventative actions and timescales for completion should be assessed by the auditors to establish whether these are appropriate to the findings. Further clarification or evidence of completion should be requested, commensurate to the risk.
- A summary assessment of the status of corrective and preventive actions should be recorded by the auditors once these have been received and assessed. An overall recommendation should be made in the final report. The summary should include whether the auditor regards the actions as satisfactory. The responsible QP should ensure that he or she, or someone to whom it is delegated, is in agreement with the overall recommendation of the final report. The QP must not release the relevant [medicinal products](#) without knowledge of a positive recommendation from the auditors. This recommendation should include the GMP compliance status of the site and whether any reduced controls on materials receipt at the finished product manufacturing site are supported by the auditors.

- A proposed re-assessment period should be recommended.
- The final report should be signed and dated by, at least, the lead auditor.

10. How should active substance auditors be qualified? H+V May 2013

Auditors should have sufficient scientific, technical and other experience to enable them to perform an adequate and thorough audit of the [active substance](#) manufacturer, as related to the planned scope of the audit. Where a proposed auditor lacks an appropriate level of direct experience in the field of [active substance](#) manufacture, he or she should undergo a documented training and assessment programme in the areas that are relevant to the audit, taking into account the auditor's anticipated role in the audit and the technologies that are likely to be encountered during the audit. Auditors must also be trained and assessed in their knowledge and understanding of EU GMP part II and in auditing techniques in general. The training and assessment should be fully documented.

The qualification and experience of contracted auditors are the same as the requirements for the manufacturing authorisation holder's own auditors.

11. What is the frequency for the routine re-inspection of an active substance manufacturer? H+V February 2015

Article 111 (1b) of Directive 2001/83/EC requires that Member States have a system of supervision including inspections at an appropriate frequency based on risk, at the premises of the manufacturers, importers, or distributors of [active substances](#) located on its territory.

In line with the document "Model for Risk Based Planning for Inspections of Pharmaceutical Manufacturers" available in the Compilation of Union Procedures, sterile and biological [active substances](#) are considered a relatively higher risk. Consequently, competent authorities may decide to submit these substances to a higher or a set inspection frequency.

12. What are the GMP requirements to be applied to the formulation of biological active substances with excipients, when described in the active substance section of a registration dossier? H+V February 2017

The [Q&As on Quality Part 1](#), address the exceptions where the formulation of an [active substance](#) can be described under CTD section 3.2.S.

For the manufacture of biological [active substances](#), Part II and Annex 2 of the GMP [guidelines](#) apply. While quality risk management principles also apply to the formulation of a biological [active substance](#), some aspects of GMP part 1 as described below are more appropriate and are expected as a minimum:

- Particular emphasis should be put on the management of the constitutive [excipients](#) of the formulated [active substance](#). Specifications should be defined for [excipients](#) according to GMP Part I., 4.14 and the monographs of the [European Pharmacopoeia](#) should be applied. The approval, maintenance and audit of [excipient](#) suppliers should be based on quality risk management, in accordance with GMP Part I., 5.29 and the EU [guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use](#). An agreement between the [medicinal product](#) manufacturer and the [excipient](#) manufacturer should be established in accordance with GMP Part I., 5.28.

The sampling of [excipients](#) used for the formulated [active substance](#) should comply with GMP Annex 8 and retention samples of [excipients](#) should be kept under the responsibility of the [medicinal product](#) manufacturer (in accordance with GMP Part I., 1.9 (viii) and GMP Annex 19).

[Excipients](#) used by the manufacturer of the formulated [active substance](#) should be included in the Periodic Quality Review (in accordance with GMP Part I., 1.10 (i)).

- Consideration should be given to the inclusion of batches of a finished [medicinal product](#) manufactured from formulated [active substances](#), stored for the maximum holding time, in the ongoing stability program of the [medicinal product](#), in accordance with GMP Annex 2, 67 and GMP Part I., 6.28.
- When outsourced, the manufacture of a formulated [active substance](#) should be managed in the same way as the outsourcing of the manufacture of an intermediate [medicinal product](#), through full application of the requirements of Chapter 7 of the GMP part I [guideline](#).

1.3. EU GMP guide part II: Basic requirements for active substances used as starting materials: GMP compliance for active substances in investigational medicinal products (IMPs)

1. Are active substances used as starting materials in the production of IMPs subject to GMP?

H July 2006

Directives [2001/82/EC](#) and [2001/83/EC](#), as amended, include obligations for manufacturing authorisation holders only to use [active substances](#) that have been manufactured in accordance with GMP. Provision is also made for inspections of active-substance manufacturers but only under certain specified circumstances.

IMPs are unaffected because the obligations of manufacturing authorisation holders in this case are laid down in [Directive 2005/28/EC](#), which does not contain corresponding requirements for [active substances](#). Furthermore, this is made clear in the introduction to part II of the [GMP guideline](#).

Part II of the [GMP guideline](#) does include a short section on new [active substances](#) to be used as starting materials for IMPs and these remain as recommendations with no mandatory force.

Nevertheless, [active substances](#) used in the manufacture of marketed products are already required to comply with GMP irrespective as to whether they may also be used in the manufacture of IMPs.

1.4. EU GMP guide annexes: Supplementary requirements: Annex 1: Manufacture of sterile medicinal products

1. How should the integrity of sterilising filters be verified? H+V June 2007

Annex 1, paragraph 85 states, 'the integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble-point, diffusive-flow or pressure-hold test.'

The filter sterilisation process may be physically stressful for the filter. For example, high temperatures during the process may cause the filter to distort, potentially leading to fluid pathways that allow the passage of particles greater than 0.2 µm in size. The performance of a filter can improve with use, as particles begin to block individual pathways and remove larger pathways that smaller particles could successfully navigate. For these reasons, filters should be tested both before use but after sterilisation and again after use.

Furthermore, testing should be performed *in situ* in order to verify the integrity of the filter complete with its housing.

2. What are the sampling requirements for sterility testing when a finished product batch of terminally sterilized medicinal product is made up of more than one sterilizer load? H+V October 2008

The sampling plan for sterility testing should take account of the definition of a batch as stated in the glossary of the [GMP guideline](#) together with the recommendations of annex 1 section 93 (section 127 in the February 2008 revision). Each steriliser load is considered to be an independent sub-batch.

Consequently, one sterility test should be performed per sub-batch. The number of samples per steriliser load should conform to [European Pharmacopoeia](#) requirements, section 2.6.1.3.

Can there be any exceptions to this rule?

For large-volume parenterals where the sterilisation cycle has been qualified with an overkill level, an alternative sampling plan in accordance with a specific internal procedure agreed with the supervisory authority can be accepted (unless already specified in the [marketing authorisation](#)).

This procedure should state the need to sample from each steriliser load including the coolest location identified during the steriliser qualification. The number of samples per load should be defined based on a risk-based approach and the overall number of samples per batch should conform to [European Pharmacopoeia](#) requirements, section 2.6.1.3. An alternative option, which would require a [variation](#) to relevant existing [marketing authorisations](#), would be to introduce a system of parametric release, thereby avoiding the need to carry out the sterility test.

3. What are the key changes in the 2008 revision of annex 1 of the EU GMP? H+V January 2010

The revision provides updated guidance on:

- classification of the environmental cleanliness of clean rooms;
- guidance on media simulations;
- guidance on capping of vials;
- bioburden monitoring prior to sterilisation.

4. The new revision to the annex includes a number of revised requirements. What steps are being taken by EU authorities to assure the consistent interpretation of the requirements of the revised annex by EU GMP inspectors during inspection? H+V Jan 2010

GMP inspectors from the EU have worked together with inspectors from [Swissmedic](#) to prepare harmonised guidance on the interpretation of the revised annex to be used during the inspection of manufacturers by their Inspectors. This document has subsequently been proposed and adopted as draft guidance by the [Pharmaceutical Inspection Cooperation Scheme](#) (PIC/S): GMP annex 1 revision 2008: Interpretation of most important changes for the manufacture of sterile [medicinal products](#).

5. For an aseptically produced product, where should bioburden monitoring take place? H+V May 2013

Update January 2019: This Q&A has been superseded by the [Guideline](#) on the sterilisation of the [medicinal product](#), [active substance](#), [excipient](#) and primary container. Please refer to this [guideline](#) for further information.

According to the EU [GMP guideline](#) (annex 1), the bioburden should be monitored before sterilisation and testing should be performed on each batch.

For routine commercial manufacturing, bioburden testing should be performed on the bulk solution, immediately before its sterile filtration. If a presterilising filter is additionally installed, then sampling for bioburden testing may be performed prior to the prefiltration, provided that no holding time is scheduled for the solution between the two filtration steps.

6. What is the maximum acceptable bioburden level? H+V May 2013

Update January 2019: This Q&A has been superseded by the [Guideline](#) on the sterilisation of the [medicinal product](#), [active substance](#), [excipient](#) and primary container. Please refer to this [guideline](#) for further information.

The specification limits for bioburden should be NMT 10 CFU/100 ml, in line with the human and veterinary notes for guidance on manufacture of the finished dosage form ([CPMP/QWP/486/95](#) and [EMA/CVMP/126/95](#)).

When a prefilter is installed, unless otherwise justified, a bioburden limit of 10 CFUs/100 ml before first filtration is achievable in principle and is strongly recommended from a GMP point of view. Higher bioburden limits should not be justified by the high capacity of two consecutive bacteria retaining filters.

However, when appropriate justification is submitted (processes involving fermentation or other biological or herbal components, use of purified water for ophthalmic preparations, etc.), a bioburden limit of higher than 10 CFUs/100 ml before prefiltration may be acceptable. In such cases, it should be demonstrated that the first filter has the capability to achieve a bioburden prior to the last filtration of NMT 10 CFUs/100 ml, in line with the notes for guidance on manufacture of the finished dosage form (CPMP/QWP/486/95 and EMA/[CVMP/126/95](#)).

7. Do I need to follow the requirements of the updated ISO 14644 part 1 standard?

Annex 1 of the EU GMP guide is currently under revision and will take account of the updated ISO standard. In the meantime, for qualification or re-qualification of clean room facilities, [medicinal product](#) manufacturers may apply the updated ISO standard with reference to Annex C (counting of macroparticles), or may continue to follow the previous ISO standard. Routine monitoring, however, should continue to be carried out in accordance with the existing Annex 1.

8. Water for injection by reverse osmosis

- [Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies - Final](#)

1.5. EU GMP guide annexes: Supplementary requirements: Annex 6: Manufacture of medicinal gases

1. What is traceability? H+V July 2010

Traceability is the ability to retrieve the history of the manufacturing and distribution operations of a batch of a [medicinal product](#).

The data recorded through the traceability system should allow efficient investigation in case an incident occurs and should allow recalls of (potentially) defective products. In the case of packaged medicinal gases, the packaging components (shells and valves) are reusable. It is therefore necessary to record additional information, in particular in relation to the use and maintenance of these components.

2. Which items should be recorded in the case of medicinal gases filled into cylinders to enable traceability? H+V July 2010

Packaging components (shells and valves)

The cylinder is the combination of the shell and its valve.

Shell

For safety reasons, shells are individually identified (specific reference). Individual traceability is therefore possible. The date of the last hydrostatic pressure test (or equivalent test) should be recorded.

Valve

Shells may be fitted with simple valves (e.g. pin-index valves) or integrated valves. Integrated valves are individually identified (individual identification reference). Individual traceability is therefore possible. This is not the case for simple valves, which mostly have only a serial number corresponding to a group of valves.

The design of integrated valves, which are medical devices, is complex. These valves are also subject to periodic preventive maintenance operations. In terms of risk, more serious incidents have been reported with cylinders having this type of valve.

Therefore:

- in the case of simple valves, the type of valve should be recorded, as well as the name of the manufacturer and the serial number, if one is available;
- in the case of integrated valves, traceability should be ensured for each valve. Records should include in particular the type of integrated valve (including the version), the individual identification reference of the valve, the name of the manufacturer, the date of the last (or next) preventive maintenance and details of any preventive maintenance performed on the valve.

Shell and valve

Each shell-and-valve combination should be traceable.

Finished product

The manufacturing batch records should include the individual identification references of the cylinders of each batch of finished product (see EU [GMP guideline](#) annex 6, section 17, (g) and (m)).

Distribution

The distribution records should include the individual identification references of the cylinders delivered to each customer.

3. What means should be implemented to ensure traceability? H+V July 2010

In practice, depending on the scale of operation, it may be difficult to ensure effective traceability without a computerised system. Use of bar codes or electronic chips on the cylinders may facilitate this. Any computerised system used to ensure traceability should conform to the requirements of annex 11 of the EU [GMP guideline](#).

4. What should be possible through the system of traceability? H+V July 2010

Should a manufacturer of a medicinal gas receive a serious complaint relating to the quality of the medicinal gas itself or the packaging components, the system in place should allow the identification of the affected cylinders and, where necessary, the recall of any affected cylinders from the market. A defect relating to packaging components may require identification of specific cylinders within a finished product batch or identification of cylinders present in a number of finished product batches in order to establish the extent of any recall required.

For example, an effective traceability system should allow effective recalls of cylinders fitted with defective valves based on:

- specific type, version or manufacturer's batch for the valves;
- maintenance and calibration operations for the valves during a specific time period.

1.6. EU GMP guide annexes: Supplementary requirements: Annex 8: Sampling of starting and packaging materials: Glycerol

1. What is the background regarding international incidents of glycerol contamination? H+V December 2007

There is a history of sporadic reports from around the world of supplies of glycerol contaminated with diethylene glycol (DEG) resulting in mortality and serious morbidity in patients receiving contaminated products.

In late 2006, DEG-contaminated glycerol in cough syrup was the cause of about 50 deaths in Panama. DEG-contaminated glycerol in paracetamol syrup was also attributed to at least 80 deaths in a similar incident in Haiti in 1995-1996. Other incidents have been reported in Argentina, Bangladesh, India and Nigeria and attributed to the deaths of hundreds of children. DEG was also responsible for a poisoning incident resulting in the death of 107 people in the United States in 1937, following ingestion of contaminated sulphanilamide elixir.

These incidents were related to both accidental cross contamination of glycerol with industrial grade materials and, in some cases, to intentional substitution.

Recent cases show the following similarities:

- pharmaceutical manufacturers of products containing contaminated glycerol did not perform full identity testing or tests to determine DEG on the glycerol raw material;
- pharmaceutical manufacturers of contaminated products relied on certificates of analysis (COAs) provided by the supplier;
- the origin of glycerine was not apparent from the COA. The COA provided with the glycerol raw material may have been a copy of the original on a distributor letterhead. The supply chain for glycerol was not readily known by the medicinal-product manufacturer because the glycerol may have been sold several times between its manufacture and the medicinal-product manufacturer.

2. How is the EU patient protected from similar contamination occurring in EU products? H+V December 2007

EU GMP requires all manufacturing companies to confirm that all its raw materials are checked on receipt to confirm their identity and quality. Competent authorities expect product manufacturers to routinely ensure that incoming samples of glycerol are tested according to the [European Pharmacopoeia](#) monograph.

The [European Pharmacopoeia](#) monograph for glycerol includes a specific limit test for diethylene glycol (0.1%).

3. Annex 8 of the GMP provides for derogations from the requirement for identity testing of every container where there is a validated supply chain. Can I use this derogation for the glycerol I purchase? H+V December 2007

It is correct that annex 8 does provide for a relaxation of identity testing of every container, but it also states that this would not normally be possible if brokers or intermediates were involved in the chain of supply.

Glycerol is a commercial article that is widely used in the food and other industries. Generally speaking, the supply chain for glycerol tends to be complex and lengthy. The involvement of brokers is common in the supply chain.

4. What steps are expected of manufacturers based in the EU when purchasing glycerol or of manufacturers based in third countries supplying glycerol-containing medicines? H+V December 2007

When designing supplier-assurance and incoming-goods-control programmes, companies should consider glycerol a higher-risk material.

Companies should be able to exhibit a good knowledge of starting material supply chains and apply this knowledge and principles of quality risk management to their programmes for supply-chain management. Inspectors will look to ensure that the basis for qualification of the supply chain is demonstrably robust for higher-risk materials such as glycerol. It is expected that identity testing and the [European Pharmacopoeia](#) limit test for DEG will be performed on each container as a matter of routine.

5. The European Pharmacopoeia limit test for DEG involves a gas chromatographic method, which may be difficult to perform on a large number of containers. H+V December 2007

This point is acknowledged and currently, alternative tests are under consideration with a view to work up a possible change to the identity tests in the monograph. The [European Pharmacopoeia](#) DEG limit test remains the official method for confirmation of compliance with the monograph.

6. Are there any considerations applicable to the pharmaceutical assessment of marketing- authorisation applications? H+V July 2008

In application dossiers for new [marketing authorisations](#) (MAs), or in case of relevant [variations](#) for existing MAs (for example, replacement of an [excipient](#) with glycerol) for [medicinal products](#) containing glycerol, confirmation of the tests applied on receipt of batches of glycerol to control the risk from potential DEG contamination in relation to the specific intended use of the product should be provided. A test for DEG content should be conducted in addition to identity testing for glycerol. A suitable control for DEG is included in the [European Pharmacopoeia](#) monograph for glycerol. Sufficient information regarding satisfactory control of this risk will be required in the dossier before approval of the MA application or [variation](#).

For existing approved [medicinal products](#), no [variation](#) application is required, except for those few specific types of [variations](#) referred to in the first paragraph. However, as a minimum, the specific [European Pharmacopoeia](#) control for DEG should be conducted along with the identity test at receipt of each batch of glycerol. The [excipient](#) is required to comply with the current [European Pharmacopoeia](#) glycerol monograph, and as the specification approved in the dossier will have been that of the [European Pharmacopoeia](#), the risk of DEG contamination will have been appropriately controlled. Compliance with this requirement will be verified during GMP inspections.

7. My company manufactures products for external use. Does this guidance apply? H+V July 2008

Where a company manufactures products for external use, and when it has justified that the presence of DEG in these products poses a low risk, the omission of the test for DEG on each container may be accepted by the supervisory authority.

EU GMP guide annexes: Supplementary requirements: Annex 8: Sampling of starting and packaging materials: Use of near-infrared (NIR) technology for container-wise identity testing

1. The registered specifications of our starting materials include conventional or pharmacopoeial methods for the confirmation of identity but we wish to use NIR to perform identity testing ...

The registered specifications of our starting materials include conventional or pharmacopoeial methods for the confirmation of identity but we wish to use NIR to perform identity testing on each container of starting materials used in the manufacture of parenteral products. Is the use of this alternative method acceptable?

Annex 8 of the [GMP guideline](#) states that the identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labeled. However, the annex goes on to say that it is improbable that a procedure could be satisfactorily validated for starting materials for use in parenteral products.

Unless [variations](#) are submitted for all affected products, the registered method for confirming identity should be performed. However, there is no restriction on the performance of additional testing and the use of NIR to confirm container-wise confirmation of identity can provide useful information.

Under these circumstances, the requirements of the [marketing authorisation](#) will be deemed to have been met by carrying out the registered method for confirmation of identity on a statistically representative composite sample when this is supplemented with NIR analysis of every container.

The NIR method should be validated in line with the recommendations of the [guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations](#).

1.7. EU GMP guide annexes: Supplementary requirements: Annex 11: Computerised systems

1. Appropriate controls for electronic documents such as templates should be implemented. Are there any specific requirements for templates of spreadsheets? H+V February 2011

Templates of spreadsheets help to avoid erroneous calculations from data remaining from previous calculations. They should be suitably checked for accuracy and reliability (annex 11 p7.1). They should be stored in a manner which ensures appropriate version control (chapter 4 p4.1).

2. What type of accuracy checks (annex 11 p 6) are expected for the use of spreadsheets? H+V February 2011

Data integrity should be ensured by suitably implemented and risk-assessed controls. The calculations and the files should be secured in such a way that formulations are not accidentally overwritten. Accidental input of an inappropriate data type should be prevented or result in an error message (e.g. text in a numeric field or a decimal format into an integer field). So-called 'boundary checks' are encouraged.

3. Are there any specific considerations for the validation of spreadsheets? H+V February 2011

Validation according to paragraph 4 of annex 11 is required at least for spreadsheets that contain custom code (e.g. Visual Basic for applications). Formulas or other types of algorithm should be verified for correctness.

4. What measures are required to ensure data security databases? H+V February 2011

Data security includes integrity, reliability and availability of data. During validation of a database-based or inclusive system, consideration should be given to:

- implementing procedures and mechanisms to ensure data security and keeping the meaning and logical arrangement of data;
- load-testing, taking into account future growth of the database and tools to monitor the saturation of the database;
- precautions for necessary migration of data (annex 11 p17) at the end of the life-cycle of the system.

5. At which phases of the system life-cycle is risk management recommended? H+V February 2011

Risk management should be applied throughout the whole life-cycle. A first risk assessment should be performed to determine the GMP criticality of the system, i.e. does the system have an impact on patient safety, product quality or data integrity? User-requirement specifications are usually developed with consideration of potential risks and form the basis for the first formal risk assessment.

Complex systems should be evaluated in further more detailed risk assessments to determine critical functions. This will help ensure that validation activities cover all critical functions.

Risk management includes the implementation of appropriate controls and their verification.

6. Are user requirements needed as part of the retrospective validation of legacy systems? H+V February 2011

The way to check whether a computerised system is fit for its intended purpose is to define user requirements and perform a gap analysis to determine the validation effort for retrospective validation. These user requirements should be verified.

7. When do I have to revalidate computerized systems? H+V February 2011

Computerised systems should be reviewed periodically to confirm that they remain in a validated state. Periodic evaluation should include, where applicable, the current range of functionality, deviation records, change records, upgrade history, performance, reliability and security. The time period for revaluation and revalidation should be based on the criticality of the system.

8. What are the requirements for storage time of electronic data and documents? H+V February 2011

The requirements for storage of electronically data and documents do not differ from paper documents. It should be ensured that electronic signatures applied to electronic records are valid for the entire storage period for documents.

9. What are the relevant validation efforts for small devices? H+V February 2011

Small devices are usually off-the-shelf pieces of equipment that is widely used. In these cases, the development life-cycle is mainly controlled by the vendor. The pharmaceutical customer should therefore reasonably assess the vendor's capability of developing software according to common standards of quality.

A vendor assessment needs to be performed and the application needs to be verified against the requirements for the intended use. From the perspective of the regulated industry, the implementation of such a device is driven by an implementation life-cycle. At minimum the following items need to be addressed:

- requirement definition for the intended use including process limitations. This should also include a statement indicating whether data are stored or transferred to another system. As per the definition of a small device, data are not stored permanently but temporarily and are not to be modified by a user. Therefore, limited user access handling is acceptable. It needs to be ensured that parameter data influencing the device's behaviour may not be altered without suitable permission;
- risk assessment, taking into consideration the intended use and the risk to patients for associated with the process supported by the small device;
- vendor assessment;
- list of available documentation from the vendor, especially those describing the methodology used and the calculation algorithm, if applicable. A vendor certificate or equivalent detailing the testing performed by the vendor may also be included;
- calibration certificate, if applicable;
- validation plan according to the risk-assessment results;
- verification testing proving that the device fulfills the requirements for the intended use. It may be equivalent to a PQ-phase.

Small manufacturing devices are sometimes only equipped with microprocessors and firmware and are not capable of high-level administration functions. Moreover, data is often transient in nature in these devices. Due to the latter there is no risk of inadvertently modifying data. An audit trail is therefore not necessary and user access may be limited to those functions of parameter control.

10. What alternative controls are accepted in case a system is not capable to generate printouts indicating if any of the data has been changed since the original entry? H+V February 2011

As long as this functionality is not supported by the supplier, it may be acceptable to describe in a procedure the fact that a print-out of the related audit trail report must be generated and linked manually to the record supporting batch release.

1.8. EU GMP guide annexes: Supplementary requirements: Annex 13

1. At what point of processing or incorporation would an active substance be considered a product intermediate and therefore an IMP? H June 2007

[Commission Directive 2001/20/EC](#) defines an IMP as 'a [pharmaceutical form](#) of an [active substance](#) or placebo being tested or used as a reference in a [clinical trial](#), including products already with a [marketing authorisation](#) but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised [indication](#), or when used to gain further information about the authorised form.'

An [active substance](#) would be considered an IMP if presented in a packaged form for use in a [clinical trial](#). Any such packaging operation could only be carried out by a site holding an IMP manufacturing authorisation.

Any form of mixing or processing the [active substance](#) with other substances would also result in the need for a manufacturing authorisation for IMPs if the resulting product is to be used in a [clinical trial](#). Physical processing such as milling of an active pharmaceutical ingredient would not constitute IMP manufacturing.

The above does not refer to reconstitution. Separate guidance on this subject is under development.

2. How can the QP of a site assure compliance with the requirements of the clinical-trial application in situations where a QP may be required to certify a batch before the application is submitted to, or accepted by, the competent authority? H June 2007

The QP of a site that is manufacturing a drug product intermediate should assure that the product is produced and controlled in compliance with the EU [GMP guideline](#), in particular the requirements of annex 13.

A product specification file should be developed with contributions from the QPs and other technical personnel of the sites involved with the other manufacturing activities of the IMP. The sponsor of the [clinical trial](#) should also be involved in this process. While this may be in a rudimentary form and contain little detail, it should be developed as knowledge of the product evolves and include

specifications for critical parameters and controls. The product specification file should be updated and evolve in line with the product development as envisaged in annex 13.

The development of the product specification file should be managed under a technical agreement or a number of technical agreements between the various manufacturing sites. These should include the QP responsible for the final certification of the product and the sponsor, if the sponsor has already been appointed. In any event, final release of the product to trial sites should take place only when the sponsor has established that the product has been manufactured in compliance with the terms of the approved clinical-trial application (as required by annex 13.44). This is defined in annexes 13.40 and 13.44: 'The sponsor should ensure that the elements taken into account by the QP when certifying are consistent with the information notified pursuant to Article 9(2) of Directive 2001/20/EC.'

3. Is it possible to perform packaging or labelling at the investigator site? H September 2007

This is normally possible only if a manufacturing authorisation has been granted to the site by the [national competent authority](#).

According to Article 9(1) of [Directive 2005/28/EC](#), the "authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall be required for both total and partial manufacture of IMPs, and for the various processes of dividing up, packaging or presentation."

However, an exemption to this obligation is foreseen in Article 9(2) of [Directive 2005/28/EC](#):

'Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member States to carry out such processes and if the IMPs are intended to be used exclusively in those institutions.' In addition, reference should be made to section 33 of annex 13 in respect of any re-[labelling](#) to extend shelf life.

4. Who is responsible for the packaging or labelling activities carried out at the investigator site? H September 2007

The sponsor has the ultimate responsibility for all trial activities performed at the investigator site, but should seek the advice of the QP of the IMP manufacturer, if possible, or the clinical-trials pharmacist at the investigator site regarding:

- adequacy of premises and equipment (storage conditions etc.);
- adequacy of written standard operating procedures;
- training of personnel involved, both on GMP requirements and any protocol specific requirements for the IMPs;
- written instructions to perform activities;
- forms to document the activities carried out;
- checks to be done;
- the keeping of retention samples;
- record-keeping.

5. Who is responsible for the transport and storage conditions when an IMP is transported from the manufacturer to the distributor or investigator sites? H May 2009

The sponsor should exercise control over the entire chain of distribution of IMPs, from manufacture or importation into the EEA, through to supply to the investigator sites, so as to guarantee that IMPs are stored, transported, and handled in a suitable manner.

When an IMP originates from a [third country](#), the importer is responsible for verifying that the transportation and storage conditions for the product are suitable. For products originating within the EEA, the manufacturer is responsible for transportation and storage conditions. The respective responsibilities of the sponsor, manufacturer, importer and, where used, distributor should be defined in a technical agreement.

6. What measures should be taken to ensure that the IMPs are kept under suitable conditions during transportation between the manufacturer or distributor and the investigator sites? H May 2009

Storage conditions during transportation should be validated or monitored using a suitable temperature-measuring device that is capable of showing fluctuations in temperature e.g. Temperature Logger. The choice of method of transport should be influenced by the nature and sensitivity of the product and should ensure timely delivery of IMPs to the investigator sites. The outer packaging should be labelled showing the final destination, the name of manufacturer or sponsor and the storage conditions required.

7. What measures should be taken to ensure that the IMPs are kept under suitable conditions during storage at the investigator sites? H May 2009

IMPs should be packaged to prevent contamination and unacceptable deterioration during storage. The sponsor should determine acceptable storage temperatures and any other required storage conditions for the IMPs (e.g. protection from light).

The sponsor should ensure that all involved parties (e.g. monitors, investigators, pharmacists, storage managers) are aware of these conditions and the actions to be taken in the event that the conditions are not met.

Where appropriate, there should be a restricted area for the storage of IMPs. The temperature of the areas and equipment used for the storage should be monitored using suitable means, such as a temperature recorder or, as a minimum, a record of the maximum and minimum temperatures, at a suitable frequency (for example, daily).

8. What written procedures should be in place at the investigator site regarding IMPs? H May 2009

The sponsor should ensure that written procedures include instructions that the investigator or institution should follow for the handling and storage of IMPs. The procedures should address adequate and safe receipt, handling, storage, where relevant any reconstitution process to be carried out before administration, retrieval of unused product from subjects, and return of unused IMPs to the sponsor (or alternative disposal, if authorised by the sponsor and in compliance with the applicable regulatory requirements).

Procedures should also give instructions on the actions to be taken when defined conditions are not met.

9. What records must be kept at the investigator site regarding the abovementioned procedures? H May 2009

The sponsor should ensure that the documents listed in chapter 8, 'essential documents for the conduct of a [clinical trial](#)' of the [guideline for good clinical practice](#) are maintained and accessible to those parties authorised to review them.

1.9. EU GMP guide annexes: Supplementary requirements: Annex 16 (Updated May 2018)

1. Can a site have more than one QP performing certification of batches?

EU legislation requires a manufacturer to have at least one QP at its disposal but a site may have more than one QP who may certify batches on behalf of the manufacturer.

2. Can there be more than one QP involved in the certification of a given batch?

Annex 16 of the EU [GMP guideline](#) gives guidance in relation to situations where different stages of manufacture of a batch take place at different manufacturing sites.

In such cases, the overall responsibility for correct manufacture of the batch lies with the QP performing final certification of the batch before release for sale. It is also possible that, at a single manufacturing site, different QPs could be responsible for certification of different stages of manufacture of the batch. However, as before, the QP performing final certification before release holds overall responsibility for manufacture of the batch in accordance with GMP and the [marketing authorisation](#).

3. In the context of handling unexpected deviations, what is included in the scope of registered specifications for medicinal products? ...

In the context of handling unexpected deviations, what is included in the scope of registered specifications for [medicinal products](#)? / What is an 'unexpected' deviation? / Does Annex 16 permit QP certification of more than one batch affected by the same unexpected deviation?

In order to satisfy the criteria in Annex 16 section 3 for handling unexpected deviations, all registered specifications for [active substances](#), [excipients](#), packaging materials and [medicinal products](#) must be met.

Registered specifications for [medicinal products](#) include in-process, bulk and finished product specifications which have been included in the MA application.

The criticality of registered in-process specifications may vary depending on the quality attribute tested, the impact to subsequent manufacturing processes and ability to test the quality attribute in

the finished product. It may therefore be possible to accept deviation from an in-process specification where risk assessment confirms that there is no impact to manufacturing process or product quality. Non-compliance with registered specifications (except where excursions from in-process specifications can be accepted based on quality risk management principles) therefore fall outside the scope of Annex 16 section 3, and the QP would not be able to certify the affected batches under the Annex 16 provisions for handling unexpected deviations.

What is an 'unexpected' deviation?

The process itself should be designed to comply with the registered requirements (fit for purpose). A deviation can be considered as 'unexpected' until the time of discovery. Where the relevant authorities have confirmed the need to avoid supply disruption, repeat deviations thereafter are no longer 'unexpected' but may be considered for QP certification and accepted while corrective and preventive action is in progress and where the provisions of Annex 16 paragraph 3.1 are met.

Planned deviations or deviations that are caused by incorrect communication between [marketing authorisation holder](#) (MAH) and manufacturers (e.g. if the MAH fails to notify the manufacturer of relevant changes to the MA) are outside the scope of the paragraph 3.1. The [marketing authorisation holder](#) should submit an application for a [variation](#) to the [marketing authorisation](#), if needed.

Does Annex 16 permit QP certification of more than one batch affected by the same unexpected deviation?

If more than one batch has already been manufactured and/or tested at the time of discovery of the unexpected deviation, then it is acceptable to consider QP certification of all these batches under the provisions of Annex 16 section 3.

Following discovery, repeated deviations from the manufacturing process and/or analytical control methods should be considered changes, and [variations](#) to the affected [marketing authorisations](#) must be submitted. In [exceptional circumstances](#) to avoid disruption to supply, it may be possible to continue QP certification while corrective and preventive action is in progress; see Q&A on what is 'unexpected' deviation above.

EU GMP guide annexes: Supplementary requirements: Annex 19: Reference and retention samples (Updated)

1. Is it necessary to retain a sufficient number of samples of each batch of a sterile medicinal product in order to carry out a sterility test on two separate occasions? H+V October 2008

For retention purposes, it is not necessary to keep the full number of samples required in table 2.6.1.3 of the [European Pharmacopoeia](#) sterility test monograph to repeat the sterility test performed for release purposes, but only a sufficient quantity to allow the carrying out, on two occasions, of a confirmatory test using the minimum quantities described in table 2.6.1.2 of the monograph.

2. In which cases does the exemption for a fully packaged unit as retention sample apply as referred to in section 2.1 of EU GMP Part I, annex 19? H+V December 2013

In which cases does the exemption for a fully packaged unit as retention sample apply as referred to in section 2.1 of EU GMP Part I, annex 19: "There may be [exceptional circumstances](#) where this requirement can be met without retention of duplicate samples e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive [medicinal products](#)?" H+V December 2013

Firstly, the supervisory authority should grant such an exemption upon request from the manufacturer. The relevant authority may agree to this when one or more of the following criteria are met:

- A batch size of less than 50 units;
- High value/low volume [medicinal products](#) and the high value price of the [medicinal product](#) as determined by each individual [competent authority](#);
- Large size of one packaged unit e.g. some veterinary pre-mixes or hospital packages.

Parallel imported/distributed [medicinal products](#) will not be granted an exemption from keeping a fully packaged unit if the products have been re-packaged. This is because the exemption refers to "duplicate samples", and in these cases no reference sample is required to be kept by the parallel distributor/importer.

On the other hand, where the secondary packaging of the source product is not opened by the parallel importer/distributor only samples of the additional packaging material used needs to be retained.

3. In those cases where the supervisory authority agrees that the criteria mentioned in the answer to question 1 are met, what should be retained instead of a fully packaged unit? H+V December 2013

The original batch specific primary packaging material with print/imprint, if any, all the original batch specific secondary packaging materials e.g. labels and leaflets with print/imprint including Braille, and dosing aids, if any, must be kept.

The use of photocopies of the fully packaged unit to replace the retention sample are not acceptable as some details e.g. braille and holograms may not show correctly.

4. Do different requirements for reference and retention samples apply for some medicinal products? H+V December 2013

The requirements pertaining to retention samples for [investigational medicinal products](#) are covered in annex 13. There may be specific national requirements for [compassionate use medicinal products](#), extemporary produced pharmacy products etc.

1.10. General GMP

1. What are the differences between EU and World Health Organization (WHO) requirements for GMP? H July 2006

EU GMP principles and [guidelines](#) are laid down in [Directive 2003/94/EC](#) (human medicines) and [Directive 91/412/EEC](#) (veterinary products). These principles and [guidelines](#) are subject to further detailed guidance in the form of the EU [GMP guideline](#) with its annexes.

WHO publishes its own GMP guidance documents.

Although EU and WHO GMP guidance documents do differ in some details, the main principles remain the same. EU requirements fulfil all the recommendations of WHO.

1.11. GMP certificates, non-compliance statements and manufacturing authorisations

1. Since Manufacturing Authorisations and GMP certificates are uploaded into the EudraGMDP database do I need a Paper copy in order to support regulatory submissions? April 2017

Documents appearing in the EudraGMDP database are uploaded by the national competent authorities through a secure network guaranteeing their authenticity. For submissions to EU authorities paper documents are not required as a reference can be made to the EudraGMDP database.

EU authorities are aware that these documents are also used to support regulatory submissions in third countries and that various additional requirements, including apostilled copies are sometimes expected. In view of the integrity of entries in the EudraGMDP database, EU authorities strongly encourage reliance on the database.

Any concerns about a certificate/authorisation in the database should be addressed to the issuing authority.

2. What is a GMP certificate, what is the difference between GMP certificates, certificates of medicinal product, also called certificates of pharmaceutical products, & certificates of suitability to the monographs of European Pharmacopoeia? H+V Jul 2006

A **GMP certificate** is a certificate issued following a GMP inspection, by the [competent authority](#) responsible for carrying out the inspection, to confirm the GMP compliance status of the inspected site.

GMP certificates are site-specific, but can be restricted to particular activities depending on the scope of the inspection (e.g., manufacturing activities related to a specific product). Directives [2001/82/EC](#) and [2001/83/EC](#), as amended state that after every GMP inspection, and within 90 days of the inspection, a GMP certificate shall be issued to a manufacturer, if the outcome of the inspection shows that the manufacturer complies with GMP.

CMPs are product-specific certificates issued by the [competent authority](#) that granted the [marketing authorisation](#). The European Medicines Agency issues CMPs on behalf of the European Commission for [centrally authorised products](#).

CMPs are issued in the context of the World Health Organization certification scheme on the quality of pharmaceutical products moving in international commerce, to confirm the marketing-authorisation status of the products. These certificates also confirm the GMP compliance status of the

manufacturing sites. CMPs are mainly used by companies to support applications to export their pharmaceutical products to countries with less-developed regulatory systems.

CEPs are certificates issued by the [European Directorate for the Quality of Medicines and Healthcare](#) (EDQM) to confirm that a certain [active substance](#) is produced according to the requirements of the relevant monograph of the [European Pharmacopoeia](#) or of the monograph on transmission spongiform encephalopathies.

CEPs can be used by companies when submitting an application for [marketing authorisation](#), and replace much of the documentation required for the [active substance](#) in the marketing-authorisation dossier. GMP inspections of active-substance manufacturers can be requested by EDQM in the context of the CEP certification scheme.

3. Does the agency issue GMP certificates? H+V July 2006

No, the [competent authority](#) responsible for carrying out the inspection issues the GMP certificate, or makes an entry of non-compliance into the [EudraGMP](#) database.

4. Which EU and EEA authorities conduct mutually recognised inspections and issue GMP certificates? H+V November 2011

All EU and EEA national competent authorities conducting inspections are obliged to enter GMP certificates in the EudraGMP database. Hence, any GMP certificate appearing in the database is mutually recognised and the database authenticates the certificate.

If a certificate cannot be found in the database, the issuing authority should be contacted.

5. How can a GMP non-compliance statement be lifted? September 2017

In principle, a GMP non-compliance statement can only be lifted following a new inspection by an EU authority that results in the issue of a GMP certificate. In practice, this can present difficulties for manufacturers located in third countries.

For sites located in third countries the GMP non-compliance statement may mean that the site is no longer listed in [marketing authorisations](#) or applications and therefore there will be no reason for a new EU inspection. However, EU inspectorates acknowledge that the manufacturer may subsequently take remedial measures to bring the site into an acceptable level of compliance. As there is no intention to convey that the site continues to operate to an unacceptable level of non-compliance and given the absence of a new inspection trigger, the issuing authority will add a clarifying remark where a non-compliance statement appears in EudraGMDP over a prolonged period of time.

1.12. Inspection coordination

1. Does the Agency perform GMP inspections? H+V July 2006

The Agency does not perform inspections. They are carried out on its behalf by the national competent authorities of the member states of the EEA, in connection with products under the centralised marketing-authorisation procedure.

2. If a site in a third country has plans to export products to the EEA, is it possible to apply for GMP inspection on a voluntary basis? H+V July 2006

Normally, the need for inspection under these circumstances is triggered by an application for a [marketing authorisation](#). It may be possible to request an inspection on a voluntary basis, but as the competent authorities will have other priorities, there is no guarantee that such a request will be met. To explore this possibility, the authorities of the Member State into which the product will be imported into the EEA should be approached. In any case, applicants are encouraged to approach the relevant authority in advance of submission in order to facilitate third-country inspection planning.

3. When a new application is submitted in the EEA and a GMP inspection is deemed necessary, which competent authority carries out the inspection? H+V July 2006

If the site is located in the EEA, the [competent authority](#) of the Member State where the site is located carries out the inspection.

For sites located in countries outside the EEA, the responsible authority for inspection (the 'supervisory authority') is the authority in whose territory the importing site is located. If the supervisory authority is not able to carry out the inspection for any reason, it can be delegated to another EEA [competent authority](#).

If there is a [mutual recognition agreement](#) (MRA) in place between the countries where the site is located and the European Community, the results of GMP inspections carried out by the MRA partner authority are normally recognised by the EU authorities.

1.13. Data integrity (New August 2016)

Data integrity

Data integrity enables good decision-making by pharmaceutical manufacturers and regulatory authorities. It is a fundamental requirement of the pharmaceutical quality system described in EU GMP chapter 1, applying equally to manual (paper) and electronic systems.

Promotion of a quality culture together with implementation of organisational and technical measures which ensure data integrity is the responsibility of senior management. It requires participation and commitment by staff at all levels within the company, by the company's suppliers and by its distributors.

Senior management should ensure that data integrity risk is assessed, mitigated and communicated in accordance with the principles of quality risk management. The effort and resource assigned to data integrity measures should be commensurate with the risk to product quality, and balanced with other quality assurance resource demands. Where long term measures are identified in order to achieve the desired state of control, interim measures should be implemented to mitigate risk, and should be monitored for effectiveness.

The following questions and answers describe foundational principles which facilitate successful implementation of existing guidance published by regulatory authorities participating in the PIC/S scheme. It should be read in conjunction with national guidance, medicines legislation and the GMP standards published in [Eudralex volume 4](#).

The importance of data integrity to quality assurance and public health protection should be included in personnel training programmes.

- [WHO - Annex 5: guidance on good data and record management practices](#)

1. How can data risk be assessed?

Data risk assessment should consider the vulnerability of data to involuntary or deliberate amendment, deletion or recreation. Control measures which prevent unauthorised activity and increase visibility / detectability can be used as risk mitigating actions.

Examples of factors which can increase risk of data integrity failure include complex, inconsistent processes with open-ended and subjective outcomes. Simple tasks which are consistent, well-defined and objective lead to reduced risk.

Risk assessment should include a business process focus (e.g. production, QC) and not just consider IT system functionality or complexity. Factors to consider include:

- Process complexity
- Process consistency, degree of automation /human interface
- Subjectivity of outcome / result
- Is the process open-ended or well defined

This ensures that manual interfaces with IT systems are considered in the risk assessment process. Computerised system validation in isolation may not result in low data integrity risk, in particular when the user is able to influence the reporting of data from the validated system.

2. How can data criticality be assessed?

The decision which data influences may differ in importance, and the impact of the data to a decision may also vary. Points to consider regarding data criticality include:

- What decision does the data influence?

For example: when making a batch release decision, data which determines compliance with critical quality attributes is of greater importance than warehouse cleaning records.

- What is the impact of the data to product quality or safety?

For example: for an oral tablet, [active substance](#) assay data is of greater impact to product quality and safety than tablet dimensions' data.

3. What does 'Data Lifecycle' refer to?

'Data lifecycle' refers to how data is generated, processed, reported, checked, used for decision-making, stored and finally discarded at the end of the retention period.

Data relating to a product or process may cross various boundaries within the lifecycle, for example:

- IT systems
 - Quality system applications
 - Production
 - Analytical
 - Stock management systems
 - Data storage (back-up and archival)
- Organisational
 - Internal (e.g. between production, QC and QA)
 - External (e.g. between contract givers and acceptors)
 - Cloud-based applications and storage

4. Why is 'Data lifecycle' management important to ensure effective data integrity measures?

Data integrity can be affected at any stage in the lifecycle. It is therefore important to understand the lifecycle elements for each type of data or record, and ensure controls which are proportionate to data criticality and risk at all stages.

5. What should be considered when reviewing the 'Data lifecycle'?

The 'Data lifecycle' refers to the:

- Generation and recording of data
- Processing into usable information
- Checking the completeness and accuracy of reported data and processed information
- Data (or results) are used to make a decision
- Retaining and retrieval of data which protects it from loss or unauthorised amendment
- Retiring or disposal of data in a controlled manner at the end of its life

'Data Lifecycle' reviews are applicable to both paper and electronic records, although control measures may be applied differently. In the case of computerised systems, the 'data lifecycle' review should be performed by business process owners (e.g. production, QC) in collaboration with IT personnel who understand the system architecture. The description of computerised systems required by EU GMP Annex 11 paragraph 4.3 can assist this review. The application of critical thinking skills is important to not only identify gaps in data governance, but to also challenge the effectiveness of the procedural and systematic controls in place.

Segregation of duties between data lifecycle stages provides safeguards against data integrity failure by reducing the opportunity for an individual to alter, mis-represent or falsify data without detection. Data risk should be considered at each stage of the data lifecycle review.

6. 'Data lifecycle': What risk should be considered when assessing the generating and recording of data?

The following aspects should be considered when determining risk and control measures:

- How and where is original data created (i.e. paper or electronic)
- What metadata is associated with the data, to ensure a complete, accurate and traceable record, taking into account ALCOA principles. Does the record permit the reconstruction of the activity
- Where is the data and metadata located
- Does the system require that data is saved to permanent memory at the time of recording, or is it held in a temporary buffer

In the case of some computerised analytical and manufacturing equipment, data may be stored as a temporary local file prior to transfer to a permanent storage location (e.g. server). During the period of 'temporary' storage, there is often limited audit trail provision amending, deleting or recreating data. This is a data integrity risk. Removing the use of temporary memory (or reducing the time period that data is stored in temporary memory) reduces the risk of undetected data manipulation.

- Is it possible to recreate, amend or delete original data and metadata;

Controls over paper records are discussed elsewhere in this guidance.

Computerised system controls may be more complex, including setting of user privileges and system configuration to limit or prevent access to amend data. It is important to review all data access opportunities, including IT helpdesk staff, who may make changes at the request of the data user. These changes should be procedurally controlled, visible and approved within the quality system.

- How data is transferred to other locations or systems for processing or storage;

Data should be protected from possibility of intentional or unintentional loss or amendment during transfer to other systems (e.g. for processing, review or storage). Paper records should be protected from amendment, or substitution. Electronic interfaces should be validated to demonstrate security and no corruption of data, particularly where systems require an interface to present data in a different structure or file format. Does the person processing the data have the ability to influence what data is reported, or how it is presented.

7. 'Data lifecycle': What risk should be considered when assessing the processing data into useable information?

The following aspects should be considered when determining risk and control measures:

- How is data processed;

Data processing methods should be approved, identifiable and version controlled. In the case of electronic data processing, methods should be locked where appropriate to prevent unauthorised amendment.

- How is data processing recorded;

The processing method should be recorded. In situations where raw data has been processed more than once, each iteration (including method and result) should be available to the data checker for verification.

- Does the person processing the data have the ability to influence what data is reported, or how it is presented;

Even 'validated systems' which do not permit the user to make any changes to data may be at risk if the user can choose what data is printed, reported or transferred for processing. This includes performing the activity multiple times as separate events and reporting a desired outcome from one of these repeats.

Data presentation (e.g. changing scale of graphical reports to enhance or reduce presentation of analytical peaks) can also influence decision making, and therefore impact data integrity.

8. 'Data lifecycle': What risk should be considered when checking the completeness and accuracy of reported data and processed information?

The following aspects should be considered when determining risk and control measures:

- Is original data (including the original data format) available for checking;

The format of the original data (electronic or paper) should be preserved, and available to the data reviewer in a manner which permits interaction with the data (e.g. search, query). This approach facilitates a risk-based review of the record, and can also reduce administrative burden for instance utilising validated audit trail 'exception reports' instead of an onerous line-by-line review.

- Are there any periods of time when data is not audit trailed;

This may present opportunity for data amendment which is not subsequently visible to the data reviewer. Additional control measures should be implemented to reduce risk of undisclosed data manipulation.

- Does the data reviewer have visibility and access to all data generated;

This should include any data from failed or aborted activities, discrepant or unusual data which has been excluded from processing or the final decision-making process. Visibility of all data provides protection against selective data reporting or 'testing into compliance'.

- Does the data reviewer have visibility and access to all processing of data;

This ensures that the final result obtained from raw data is based on good science, and that any data exclusion or changes to processing method is based on good science. Visibility of all processing information provides protection against undisclosed 'processing into compliance'.

9. 'Data lifecycle': What risk should be considered when data (or results) are used to make a decision?

The following aspects should be considered when determining risk and control measures:

- When is the pass / fail decision taken;

If data acceptability decisions are taken before a record (raw data or processed result) is saved to permanent memory, there may be opportunity for the user to manipulate data to provide a satisfactory result, without this change being visible in audit trail. This would not be visible to the data reviewer.

This is a particular consideration where computerised systems alert the user to an out of specification entry before the data entry process is complete (i.e. the user 'saves' the data entry), or saves the record in temporary memory.

10. 'Data lifecycle': What risk should be considered when retaining and retrieving data to protect it from loss or unauthorized amendment?

The following aspects should be considered when determining risk and control measures:

- How / where is data stored;

Storage of data (paper or electronic) should be at secure locations, with access limited to authorised persons. The storage location must provide adequate protection from damage due to water, fire, etc.

- What are the measures protecting against loss or unauthorised amendment;

Data security measures should be at least equivalent to those applied during the earlier Data lifecycle stages. Retrospective data amendment (e.g. via IT helpdesk or data base amendments) should be controlled by the pharmaceutical quality system, with appropriate segregation of duties and approval processes.

- Is data backed up in a manner permitting reconstruction of the activity;

Back-up arrangements should be validated to demonstrate the ability to restore data following IT system failure. In situations where metadata (including relevant operating system event logs) are stored in different file locations from raw data, the back-up process should be carefully designed to ensure that all data required to reconstruct a record is included.

Similarly, 'true copies' of paper records may be duplicated on paper, microfilm, or electronically, and stored in a separate location.

- What are ownership / retrieval arrangements, particularly considering outsourced activities or data storage;

A technical agreement should be in place which addresses the requirements of Part I Chapter 7 and Part II Section 16 of the GMP guide.

11. 'Data lifecycle': What risk should be considered when retiring or disposal of data in a controlled manner at the end of its life?

The following aspects should be considered when determining risk and control measures:

- The data retention period

This will be influenced by regulatory requirements and data criticality. When considering data for a single product, there may be different data retention needs for pivotal trial data and manufacturing process / analytical validation data compared to routine commercial batch data.

- How data disposal is authorised

Any disposal of data should be approved within the quality system and be performed in accordance with a procedure to ensure compliance with the required data retention period.

12. Is it required by the EU GMP to implement a specific procedure for data integrity?

There is no requirement for a specific procedure, however it may be beneficial to provide a summary document which outlines the organisations total approach to data governance.

A compliant pharmaceutical quality system generates and assesses a significant amount of data. While all data has an overall influence on GMP compliance, different data will have different levels of impact to product quality.

A quality-risk management (ICH Q9) approach to data integrity can be achieved by considering data risk and data criticality at each stage in the Data lifecycle. The effort applied to control measures should be commensurate with this data risk and criticality assessment.

The approach to risk identification, mitigation, review and communication should be iterative, and integrated into the pharmaceutical quality system. This should provide senior management

supervision and permit a balance between data integrity and general GMP priorities in line with the principles of [ICH Q9](#) & [Q10](#).

13. How are the data integrity expectations (ALCOA) for the pharmaceutical industry prescribed in the existing EU GMP relating to active substances and dosage forms published in Eudralex volume 4?

The main regulatory expectation for data integrity is to comply with the requirement of ALCOA principles. The table below provide for each ALCOA principle the link to EU GMP references (Part I, Part II and Annex 11):

	Basic Requirements for Medicinal Products (Part I): Chapter 4⁽¹⁾ / Chapter 6⁽²⁾	Basic Requirements for Active Substances used as Starting Materials (Part II) : Chapter 5⁽³⁾ / Chapter 6⁽⁴⁾	Annex 11 (Computerised System)
Attributable (data can be assigned to the individual performing the task)	[4.20, c & f], [4.21, c & i], [4.29, e]	[6.14], [6.18], [6.52]	[2], [12.4], [15]
Legible (data can be read by eye or electronically and retained in a permanent format)	[4.1], [4.2], [4.7], [4.8], [4.9], [4.10]	[5.43] [6.11], [6.14], [6.15], [6.50]	[7.1], [9], [10], [17]
Contemporaneous (data is created at the time the activity is performed)	[4.8]	[6.14]	[12.4], [14]
Original (data is in the same format as it was initially generated, or as a 'verified copy', which retains content and meaning)	[4.9], [4.27], [Paragraph "Record"]	[6.14], [6.15], [6.16]	[8.2], [9]
Accurate (data is true / reflective of the activity or measurement performed)	[4.1], [6.17]	[5.40], [5.45], [6.6]	[Paragraph "Principles"], [5], [6], [10], [11]

¹Chapter 4 (Part I): Documentation

²Chapter 6 (Part I): Quality control

³Chapter 5 (Part II): Process equipment (computerized system)

⁴Chapter 6 (Part II): Documentation and records

14. How should the company design and control their paper documentation system to prevent the unauthorised recreation of GMP data?

The template (blank) forms used for manual recordings may be created in an electronic system (Word, Excel, etc.). The corresponding master documents should be approved and controlled electronically or in paper versions. The following expectations should be considered for the template (blank) form:

- have a unique reference number (including version number) and include reference to corresponding SOP number
- should be stored in a manner which ensures appropriate version control
- if signed electronically, should use a secure e-signature

The distribution of template records (e.g. 'blank' forms) should be controlled. The following expectations should be considered where appropriate, based on data risk and criticality:

- enable traceability for issuance of the blank form by using a bound logbook with numbered pages or other appropriate system. For loose leaf template forms, the distribution date, a

- sequential issuing number, the number of the copies distributed, the department name where the blank forms are distributed, etc. should be known
- Distributed copies should be designed to avoid photocopying either by using a secure stamp, or by the use of paper colour code not available in the working areas or another appropriate system.

15. What controls should be in place to ensure original electronic data is preserved?

Computerised systems should be designed in a way that ensures compliance with the principles of data integrity. The system design should make provisions such that original data cannot be deleted and for the retention of audit trails reflecting changes made to original data.

16. Why is it important to review electronic data?

In the case of data generated from an electronic system, electronic data is the original record which must be reviewed and evaluated prior to making batch release decisions and other decisions relating to GMP related activities (e.g. approval of stability results, analytical method validation etc.). In the event that the review is based solely on printouts there is potential for records to be excluded from the review process which may contain un-investigated out of specification data or other data anomalies. The review of the raw electronic data should mitigate risk and enable detection of data deletion, amendment, duplication, reusing and fabrication which are common data integrity failures.

Example of an inspection citing:

Raw data for HPLC/GC runs which had been invalidated was stored separately to the QC raw data packages and had not been included in the review process.

In the above situation, the procedure for review of chromatographic data packages did not require a review of the electronic raw data or a review of relevant audit trails associated with the analyses. This led to the exclusion of records from the review process and to lack of visibility of changes made during the processing and reporting of the data. The company was unable to provide any explanation for the data which had been invalidated.

17. Is a risk-based review of electronic data acceptable?

Yes. The principles of quality risk management may be applied during the review of electronic data and review by exception is permitted, when scientifically justified.

Exception Reporting is used commonly as a tool to focus the review of electronic data such as (but not limited to) electronic batch records. Exception reporting rapidly highlights to the reviewer one of the most critical elements of batch review, i.e. the exceptions. The level of review of the full electronic batch record can vary based on the exceptions as well as the level of confidence and experience with a particular process. Appropriate testing and validation must be completed for the automated system and the output Batch Exception Report to ensure its functionality meets the business and regulatory requirements as per GMP.

18. What are the expectations for the self-inspection program related to data integrity?

Ongoing compliance with the company's data governance policy/procedures should be reviewed during self-inspection, to ensure that they remain effective. This may also include elements of the Data lifecycle discussed in Q3-Q9.

19. What are my company's responsibilities relating to data integrity for GMP activities contracted out to another company?

Data integrity requirements should be incorporated into the company's contractor/vendor qualification/assurance program and associated procedures.

In addition to having their own data governance systems, companies outsourcing activities should verify the adequacy of comparable systems at the contract acceptor. The contract acceptor should apply equivalent levels of control to those applied by the contract giver.

Formal assessment of the contract acceptors competency and compliance in this regard should be conducted in the first instance prior to the approval of a contractor, and thereafter verified on a periodic basis at an appropriate frequency based on risk.

20. How can a recipient (contract giver) build confidence in the validity of documents such as Certificate of Analysis (CoA) provided by a supplier (contract acceptor)?

The recipient should have knowledge of the systems and procedures implemented at the supplier for the generation of the CoA. Arrangements should be in place to ensure that significant changes to

systems are notified and the effectiveness of these arrangements should be subjected to periodic review.

Data related to activities which are outsourced are routinely provided as summary data in a report format (e.g. CoA). These summary documents are reviewed on a routine basis by the contract acceptor and therefore the review of data integrity at the contract acceptor site on a regular periodic basis (e.g. during on-site audit) takes on even greater significance, in order to build and maintain confidence in the summary data provided.

21. What are the expectations in relation to contract calibration service providers who conduct calibrations on-site and/or off-site? Are audits of these companies premises required?

Using the principles of QRM to assess data criticality and risk, the company should include assessment of data governance systems implemented by the service provider when making decisions on service contracts. This may be achieved by on-site audit or desk-based assessment of information submitted by the service provider.

22. What is expected of my company in the event that one of my approved contractors is issued with a warning letter/statement of non-compliance concerning data integrity, from a regulatory authority?

What is expected of my company in the event that one of my approved contractors (e.g. active substancemanufacturer, finished product manufacturer, quality control laboratory etc.) is issued with a warning letter/statement of non-compliance concerning data integrity, from a [regulatory authority](#)? It is considered that the company should evaluate the risk to its products manufactured/released using the principles of quality risk management. Risk assessments should be made available to Inspectors, on request.

Depending on the outcome of the risk assessment, appropriate action should be taken which may entail delisting the contractor from the approved contractor list. In the event that abnormal disruption in supply may result from a contractor compliance situation, relevant regulatory authorities should be consulted in this regard.

23. Where does my company's responsibility begin and end in relation to data integrity aspects of the supply chain for medicinal products?

All actors in the supply chain play an important part in overall data integrity and assurance of product quality.

Data governance systems should be implemented from the manufacture of starting materials right through to the delivery of [medicinal products](#) to persons authorised or entitled to supply [medicinal products](#) to the public.

Relative responsibilities and boundaries should be documented in the contracts between the relevant parties. Final responsibility of ensuring compliance throughout the supply chain rests with batch certifying QP.

1.14. GDP requirements (New June 2018)

Is it acceptable that storage conditions are not monitored for medicinal products which do not have any predefined storage conditions on the outer packaging?

No. According to the [Guideline on declaration of storage conditions \(CPMP/QWP/609/96 Rev. 2\)](#) , [marketing authorisation holders](#) have to provide **stability data** for storage conditions at 25°C / 60% relative humidity (RH), or 30°C / 65% RH (long term) and 40°C / 75% RH (accelerated), in order to justify not including a statement in the [medicinal product labelling](#).

This stability data is generated according to the temperature and humidity conditions of climate zone I (temperate) and II (Mediterranean/subtropical) in Europe. For more information, see the [World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations forty-third report, Annex 2: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products](#).

No [labelling](#) statement means that controls should be in place to maintain conditions relevant to climate zones I and II. Consequently, the **temperature should be monitored** during storage and transport. Appropriate limits should be set for temperature monitoring to ensure that product stability is not adversely affected.

1.15 Active substance registration (New July 2018)

What are the registration requirements for manufacturers and importers of active substances used in medicinal products for human use?

The requirements for registration of manufacturers and importers of [active substances](#) (and [active substance](#) intermediates, i.e crude [active substances](#) or other [active substance](#) intermediates, the manufacturing of which is described in a regulatory dossier) as required under Article 52a of Directive 2001/83/EC is summarised in the table below.

	Active substances for human use	Active substance intermediates for human use
Manufacturer	Yes	Yes
Registration Distributor	Yes	No
Importer	Yes	No

1.16. EU GMP guide part IV: GMP requirements for advanced therapy medicinal products (ATMP): Guidelines on GMP specific to ATMPs (New June 2019)

24 April 2019
EMA/CAT/224381/2019

Questions and answers on the use of out-of-specification batches of authorised cell/tissue-based advanced therapy medicinal products

1. What is the pathway for the exceptional administration of out-of-specification (OOS) batches of a cell/tissue based advanced therapy medicinal products (ATMPs) that have been granted a marketing authorisation?

In the exceptional circumstances set out in Section 11.5 of the Guidelines on GMP for ATMPs¹, the administration of a cell/tissue-based ATMP that does not comply with the specifications set out in the marketing authorisation may be considered to avoid an immediate significant hazard to the patient. The supply of an OOS batch can only occur when the conditions laid down in Section 11.5 of the above-mentioned Guidelines are met, in particular that the manufacturer provides an evaluation of the risks to the treating physician and that the supply of the batch is requested by the treating physician after having considered the specific condition of the patient and the evaluation of the risks provided by the manufacturer.

The manufacturer of the OOS batch should always be at the centre of the investigation of the root causes leading to the OOS result and of the evaluation of the risks. In cases where the manufacturer, importer and marketing authorisation holder (MAH) are different legal entities, there should be a written agreement between the parties which lays down the respective roles including also with regard to the communication with the treating physician and competent authorities.

2. Who should be notified and when?

When an OOS batch of a cell/tissue-based ATMP that has been granted a marketing authorisation is detected, the priority for the MAH/manufacturer/importer should be to immediately inform the treating physician and to conduct an evaluation of risks.

The competent authorities that should be informed when a patient has been administered an OOS batch are the Supervisory Authority (Competent Authority responsible for granting the manufacturing authorisation to the site manufacturing or importing the medicinal product within the European Union) and EMA (as the body responsible for the scientific evaluation and oversight of ATMPs that have been granted a marketing authorisation).

The manufacturer/importer/MAH should inform the Supervisory Authority and EMA whenever an OOS batch has been supplied for administration to a patient in the EU. Following the supply of the product

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at the request of the treating physician, it is expected that the manufacturer/importer/MAH informs at the same time the Supervisory Authority and EMA within 48 hours.

3. How should the manufacturer/importer/MAH notify the EMA of the OOS batch(es)?

The manufacturer/importer/MAH should notify EMA of any OOS batch(es) by submitting a Quality Defect report². The risk evaluation should be attached, including the results of the batch analysis. EMA will inform the CAT Rapporteur of the authorised product of each OOS. If a trend is detected, the need for regulatory actions will be considered.

4. Are National Competent Authorities involved?

ATMPs are centrally authorised products and, once authorised, fall under the oversight of EMA and the Supervisory Authority for the importing into the EU/manufacturing site. The manufacturer/importer/MAH should contact the National Authority of the treating site(s) to check if they have to be informed. Where required, the information should be provided to National Competent Authorities at the same time as the submission to the supervisory authority and EMA (see question 2).

5. Are there any other obligations or expectations that the manufacturer/importer and MAH have to follow in case of an OOS batch of a cell/tissue based ATMP that has been granted a marketing authorisation?

The obligations of the manufacturer/importer are not waived. Although it is acknowledged that the QP cannot certify the OOS batch, he/she has to ensure that the verifications on the batch have been performed. It follows that the import into the EU of OOS batches should follow standard import procedures.

Additionally, the manufacturing/importing site should - as a minimum - keep records of all details concerning the manufacture, testing, transport and storage of the product, the request of the treating physician and the analysis of the risks provided by the MAH / manufacturer. The records on the investigation of the OOS result(s) and associated risk assessment in relation to the potential impact on product quality should also be available.

The obligations of the MAH are also not waived. Therefore, pharmacovigilance reporting obligations or specific additional obligations to follow-up patients treated with the ATMP (*e.g.* registry) continue to apply in respect of OOS batches.

6. What information should be provided to the patient?

The patient should be informed about the OOS ATMP the patient is going to receive. The information that shall be provided to the patient is governed by national legislation of the treating site.

The information to patients should be provided in lay language.

It is stressed that document(s) designed to inform patients can neither transfer any responsibilities to the patient nor discharge the responsibilities of the MAH or the manufacturer.

19 July 2019
EMA/354272/2019

Questions and answers on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country

1. What are the obligations of the Qualified Person (QP) regarding testing of batches for ATMPs imported into EU?

In the case of an authorised ATMP imported from a third country, the QP has to ensure that each batch has been manufactured in accordance with Good Manufacturing Practice and that the quality is in accordance with the terms of the marketing authorisation. Imported ATMP batches have to be re-tested upon importation into the EU, as required by Article 51(1)(b) of Directive 2001/83/EC.

Article 51(2) of Directive 2001/83/EC, makes provision for the Qualified Person certifying the imported batch to rely on controls conducted in a third country (batch release testing in accordance with the

terms of the marketing authorisation) where the product has been manufactured and tested in a country having a relevant mutual recognition agreement (or equivalent arrangements) (MRA) with the EU.

The possibility to rely on controls conducted outside of the EU (where no relevant MRA on GMP is in place) is exceptional and cannot be applied beyond the specific scenarios described in the GMP Guideline for ATMPs.

2. In which cases can the exemption from EU batch re-testing for imported ATMPs be granted?

The exemption from re-testing batches upon import into the EU for ATMPs may only be granted where the conditions laid down in paragraph 11.17 of the EU GMP guideline for ATMPs¹ are met, specifically:

1 Eudralex Volume 4 Good manufacturing practice "Guideline on Good manufacturing practice specific to Advanced Therapy Medicinal Products", at paragraph 11.17

1) limited amount of material available;

Or

2) short shelf-life;

Questions and answers on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country EMA/354272/2019 Page 2/3

And

3) the testing in the third country should be conducted in GMP-certified facilities.

This exceptional exemption is primarily foreseen for imported patient-specific ATMPs (e.g. autologous product).

Technical difficulties in the transfer of analytical methods from third countries to the EU cannot be used as a basis to accept an exemption from re-testing of batches imported into the EU.

Requests for an exemption from batch re-testing in the EU for an imported ATMP should be supported by a justification and, where applicable, scientific data to substantiate the claim made (please refer to Question 3 below). The request and corresponding justification will be assessed by the CAT/CHMP during the evaluation of the marketing authorisation procedure.

As the EU GMP guideline for ATMPs requires that "*in such cases, the testing in the third country should be conducted in GMP-certified facilities (in the case of authorised ATMPs)*", a GMP pre-approval inspection is expected to be triggered unless a valid GMP certificate is available from an inspection carried out by an EEA competent authority, on the same or similar category of testing.

Applicants intending to rely on paragraph 11.17 of the GMP for ATMPs Guidelines to request an exemption from re-testing of batches imported into the EU are strongly advised to proactively consult with EMA early in product development.

3. Which data should be submitted in the marketing authorisation application to the EMA in order to justify the exemption from batch re-testing in the EU of imported ATMPs?

To substantiate the request, the applicant/MAH should provide at least the following data in the initial marketing authorisation application:

- total batch size and number of units required for batch release testing;
- available stability data and proposed shelf life;
- analytical sampling plan;
- a GMP certificate issued by an EEA Competent Authority relevant to the particular category of testing at the facility located in the third country.

Changes to the particulars of the marketing authorisation, for instance upscaling of batch size, may annul the exemption granted if the ATMP no longer meets the criteria set out in the EU GMP guideline for ATMPs. In such cases, batch release testing would be required to be conducted in the EU, in accordance with Article 51(1)(b) of Directive 2001/83/EC.

4. What are the obligations of the Qualified Person for the batch release of imported batches exempted from re-testing in the EU?

The general obligations of the QP as laid down into the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products² are not waived for imported ATMPs subject to exemption from re-testing in the EU as regards to the requirements for performing the batch release. However, only in case of a granted exemption, the EU QP certifying the imported batch may rely on quality control testing in accordance with the terms of the marketing authorisation performed in a third country. The EU QP should have access to additional manufacturer documents (e.g. raw analytical data), as needed, in order to certify the imported batches.

2. MHRA (Europe/UK)

2.1. Quality Risk Management

1. Do all inspections cover the quality risk management process?

Yes, quality risk management (QRM) is a requirement of Chapter 1 of the EU GMP Guide Part I, II and III. All manufacturing authorisation holders, third country manufacturing sites, blood establishments, blood banks and active pharmaceutical ingredient manufacturers must have a system for QRM. Inspectors will review the QRM system as part of the Quality Systems section of the inspection (along with complaints, recalls, deviations, and product quality reviews etc). Additionally, inspectors may review specific risk assessments when encountered during inspection. Inspectors will allocate time commensurate with their perceived significance of the risk and if necessary request the company to produce a formal summary of the risk assessment, key decisions and conclusions or take copies of risk assessments for further consideration outside the inspection.

2. How will deficiencies be categorised?

As with other areas of inspection, deficiencies will be categorised dependent on the significance of the findings. Typically complete lack of a system should be classed as a major deficiency, while lesser deviations within a system would be classed as other. Critical deficiencies may reference QRM where risk assessments have inappropriately supported release of products that pose a threat to patient safety. QRM deficiencies may be grouped with other quality systems deficiencies under a quality systems heading. As always factual statements of what are seen as deficiencies will be clearly recorded.

3. Should a company have a procedure to describe how it approaches QRM related to manufacture and GMP?

Yes, the procedure should be integrated with the quality system and apply to planned and unplanned risk assessments. It is an expectation of Chapter 1 that companies embody quality risk management. The standard operating procedure (SOP) should define how the management system operates and its general approach to both planned and unplanned risk management. It should include scope, responsibilities, controls, approvals, management systems, applicability, and exclusions.

4. Is it acceptable to link quality risk management with cost saving measures?

The expectation of QRM is to assess risks to the medicinal product and patient and manage these to an acceptable level. It is appropriate for companies to assess their control systems to implement the optimum controls to ensure product quality and patient safety. If this can be achieved in a more cost effective manner while maintaining or reducing risk to the product and patient then this is acceptable. However inappropriate risk assessment and mitigation in order to achieve cost savings is not appropriate.

5. Should sites have a formal risk register and management process?

There is no formal requirement in Annex III for a risk register however MHRA consider that it is helpful to the implementation and ongoing management of QRM that a risk register is established. A risk register (or equivalent title document) should list all key risks identified by the organisation, summarise how these have been mitigated and record the current risk level. They should be considered in the same context as index/lists of complaints received or deviations recorded and as such should have the following attributes:

- Record the source of the risk e.g. complaint, supplier management, change control etc.
- Record a unique identifying number for the risk
- Summarise the risk
- Record the current risk level
- Summarise current status
- Identify if the risk is considered finite (one off) or dynamic (ongoing risk) and thus what ongoing review is required.
- Can be paper based or electronic

A management process should be in place to review QRM and the findings and status from risk assessments – this may be incorporated into the quality management review process. The use of a risk register and management review should enable the owner to view the risks across all areas and ensure that QRM is under control and the cumulative impact of risks are understood.

6. What tools are acceptable to use in quality risk management?

There is no definitive list although a number of examples are given in EU GMP Part III. In some cases combinations of tools or other approaches may be seen. The important criterion is for the tool used to support the key attributes of a good risk assessment (see below).

7. Do formal tools and a full report have to be issued for every risk assessment?

As stated in Chapter 1 of the EU GMP guide ‘...the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk’. As such expectations of inspectors will be pragmatic regarding the degree of formality that is required, however appropriate evidence should be available of what has been done and as such a written output must be retained. Inspector’s pragmatism will be directly related to the nature of the risk with increasingly more formality and detail required for more significant risk (risk being the probability of occurrence of harm and the severity of that harm, often supplemented by the ability to detect the potential harm occurring).

8. What are the key attributes of a good risk assessment?

The following key attributes should be observed (mindful of the risk significance addressed in the previous question):

- clearly identify the process being assessed and what it is attempting to achieve, ie what the harm/risk is and what the impact could be on the patient
- be based on systematic identification of possible risk modes e.g. as per Failure Mode and Effects Analysis (FMEA)
- take full account of current scientific knowledge
- be facilitated by people with experience in the risk assessment process and the process being risk assessed
- use factual evidence supported by expert assessment to reach conclusions
- do not include any unjustified assumptions
- identify all reasonably expected risks – simply and clearly along with a factual assessment and mitigation where required
- be documented to an appropriate level and controlled/approved
- ultimately be linked to the protection of the patient
- should contain objective risk reduction plans.

9. What is the difference between a planned and unplanned risk assessment?

A planned risk assessment is one that is conducted in advance of conducting an activity, either before any activity is conducted or before further activity is conducted. This would often allow quality to be built in to activities and risk reduced (quality by design) e.g. design of facilities for manufacture of cytotoxic products or organisation/design of a label printing room. An unplanned risk assessment is one that is conducted to assess the impact of a situation that has already occurred, eg impact of a deviation from normal ways of working.

10. Should we expect there to be no risk to patient safety as a conclusion to a risk assessment?

In reality there is always a degree of risk in all situations but risk reduction measures should minimise the probability and severity to an acceptable level of assurance. The degree of risk tolerated very much depends on the circumstances, the proximity to the patient and other controls that may follow the process being assessed before the product is used by the patient. It should be expected that risk mitigation plans are identified and implemented where any risk to patient safety is posed. Companies should take a holistic view and be mindful that critical issues often occur where multiple failures in systems occur together so risk reduction plans should be sufficiently robust to tackle such potential.

Inspectors will be assessing if risk assessments underrate either the probability, severity or detection of occurrences in order to make it appear that there is minimal risk to the patient. The factual evidence behind statements may be challenged.

The impact should not consider the financial impact on a site/company to the detriment of the patient.

11. Are any areas out of bounds for risk assessment?

It would be unacceptable for risk assessment to conclude that statutory, regulatory or GMP requirements should not be followed or are not appropriate eg risk assessment could not conclude that it was appropriate for licensed products to be released by someone who was not a qualified person (QP). Otherwise risk assessments can be used within GMP systems as a tool to identify, quantify and minimise and control risk to patient safety.

12. How should risk assessments be controlled?

Risk assessments should be controlled within a defined document management system. If risk assessments are conducted to justify controls for an ongoing process then the assessments should be subject to change control and periodic review, e.g. line clearance risk assessment. Frequency of review should be appropriate for the nature of the process. Such risk assessments should be seen as living documents that are visible and subject to change as and when required. Risk assessments that were conducted as one off activities to assess a situation that will not recur need not be controlled in a 'live' manner but must be documented, approved and retained e.g. assessment of a temperature excursion on storage of a batch of starting material. Such 'one off' activities should be controlled as live documents if any conclusions are to be used in any future excursions. Ultimately these may then need to be reviewed in light of experience or developments.

13. Do risk assessments have to be supported by factual evidence or can they just use professional judgment?

There should be factual evidence recorded to support any conclusions drawn e.g. plant design details in controlling cross contamination - an unsupported assumption that the plant must be suitably designed as we have used it for 10 years or we've had a standard operating procedure (SOP) for five years so it must be suitable is a weak approach that may be unfounded and must be challenged by those conducting risk assessments. Professional judgment should be used in interpretation of factual evidence but must be subject to justification.

14. Scoring in risk assessments is subjective, is there danger that risk assessments may be manipulated to draw desired conclusions?

The scoring system and trigger points for risk reduction are subjective. However as important as the scores in risk assessments is the rationale for the score. If supported by factual evidence it should be more obvious what risk control and reduction measures are required – the control/reduction measure is as important as the score assigned. Companies should not score risks in a blinkered manner without considering the factual causes, probability of detection and severity. Inspectors will be alert to improper use of risk assessments to condone poor practice or exclude patient risk.

15. Is it acceptable to allow external consultants to participate in site risk assessments?

It may be appropriate for consultants to provide support for risk assessments where they can provide specific expertise or knowledge. Their role in the risk assessment should be clear. The reason for delegation and resultant accountability must be understood. Inspectors will expect sites to demonstrate that delegation was effective and that appropriate skill, knowledge, local knowledge and local accountability was appropriate for the life cycle of the risk assessment. A technical agreement may be appropriate with the consultant where GMP responsibility is assumed.

16. Is it acceptable to allow contract staff to participate in site risk assessments?

It would be usual for contract staff, e.g. contract QPs to lead or participate in risk assessments. The extent of involvement as responsibility/accountability must be documented in the technical agreement between the individual and the organisation.

2.2. Out of Specification

1. Has the MHRA produced any guidance?

Out of specification investigations (290Kb)

2. Why is there a need to conduct an investigation of an OOS test result if the decision has been taken to reject the batch?

A phase 1 investigation should always be conducted in order to try and establish an assignable cause and determine whether any other batches may be affected. In determining the assignable and root cause of the problem appropriate corrective and preventative actions can be undertaken

3. Who should investigate OOS?

Both the manufacturers and the laboratories should be involved in the investigation.

4. How is an out of trend result handled?

Results that are out-of-trend (OOT) should be handled similarly to OOS investigations.

5. Is it acceptable for a contract laboratory (contract acceptor) to use the contract givers' procedure when handling OOS results?

There is an expectation that contract acceptors should follow their own procedures and that these should be flexible enough to accommodate the needs of the contract giver.

It is assumed that the contract giver has assessed the contract acceptor's procedure for handling of out of specification results and has agreed it as being suitable for their intended purpose. Any issues should have been discussed prior to conducting any analysis

6. How is a meaningful OOS investigation conducted?

A meaningful OOS investigation should be thorough, timely, unbiased, well-documented, and scientifically defensible.

7. At what point should a manufacturing investigation be initiated?

This should be initiated as part of the phase II investigation and as a result of the phase 1 investigation not revealing a conclusive laboratory error or the error remains unclear with no assignable cause.

8. What should be done if unexpected results are obtained and there is no obvious explanation?

These are also referred to as aberrant/anomalous. Preliminary laboratory investigation should occur and they should be handled similarly to OOS investigations.

9. Under what circumstances could test results become invalid?

If there is clear evidence of a determinant error. Or where the system suitability/method validity checks fail.

10. What should be done in the case where part way through testing the analyst realises there is an error?

If there is clear evidence of the error and it can be corrected without compromising the results or the validity of the method; for example a dilution error 20 ml volumetric flask used instead of a 25 ml volumetric then it should be handled as a deviation and the results are still valid. If there is any doubt as to the impact of the error which could mean the results may not be accurate, for example sample spillage then the testing should be stopped and the issue handled as a deviation to explain what happened.

11. When should the analyst inform the supervisor that they have an OOS results?

In the first instance, the analyst will be responsible for the preliminary laboratory investigation. This will involve them checking their work and confirming that there is no obvious error prior to informing their supervisor and initiating a phase 1 investigation. This should be done within a timely manner, preferably on the day of generating the results.

12. What should be done when the phase 1 investigation does not reveal an assignable cause or evidence of error remains unclear?

A phase II investigation is initiated, which will involve communication between the laboratory and the manufacturer/contract giver. The decision to undertake any further testing should be agreed and approved within a pre-defined testing plan.

13. How many repeat tests should be conducted?

The minimum number of retests should be documented within the procedure and be based upon scientifically sound principles. Any statistical review with regards to %RSD and repeatability should relate to the values obtained during method validation, i.e. accuracy, precision and intermediate precision. The number of retests should be statistically valid.

14. What should be done if after retesting there is a combination of OOS results and pass results?

All results should be reported unless there is clear evidence of a determinant error or an assignable cause that could invalidate any of the results.

15. What should happen if the OOS investigations are inconclusive?

The certifying qualified person should fully consider all of the information prior to making any decisions as to the final disposition of the batch. Any decision to release a batch where OOS results have not been invalidated should come only after a full investigation has shown that the OOS result does not reflect the quality of the batch. In making such a decision quality assurance and the Qualified Person should always err on the side of caution.

16. When is it acceptable to average test results?

Where averaging of separate tests is appropriately specified by the test method, a single averaged result can be reported as the final test result. The validity of averaging depends upon the sample and its purpose. Using averages in the case of microbiological assay can provide more accurate results because of the innate variability of the microbiological test system. For example the kinetic scan of individual wells or endotoxin data from a number of consecutive measurements or with HPLC consecutive replicate injections from the same preparation where the determination is considered one test one result.

17. When is it not acceptable to average test results?

Averaging cannot be used in cases when testing is intended to measure variability within the product, such as powder blend/mixture uniformity or dosage form content uniformity. In the context of additional testing performed during an OOS investigation, averaging the result(s) of the original test that prompted the investigation and additional retest or resample results obtained during the OOS investigation is not appropriate because it hides variability among the individual results.

18. At what stage should retesting occur?

Retesting occurs at phase II of the investigation. The initial hypothesis testing can involve re-measurement of the original preparation or working solutions, however retesting is when the original sample or composite sample is used to perform analysis. Hypothesis testing and retesting are part of the phase II investigation. Only if the original sample is depleted or compromised should a new sample be used.

19. At what stage should re-sampling occur?

Re-sampling at phase II of the investigation should only occur if the original sample is depleted or compromised and the same method should be used. If the investigation determines that there were errors with the initial sampling method only then should a new accurate sampling method be developed, qualified and documented.

20. When is it appropriate to use outlier tests?

Statistical analysis for Outlier test results can be as part of the investigation and analysis. However for validated chemical tests with relatively small variance and that the sample was considered homogeneous it cannot be used to justify the rejection of data.

3. ECA Foundation

3.1 EU GMP Annex 11: Computerised System

Chapter 1 – Risk Management

Speakers:

Klaus Eichmüller, Local Administration of Upper Bavaria (Regierung von Oberbayern)

Dr Jörg Schwamberger, Merck KGaA

Annex 11: "Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system."

What can elements of risk management contribute towards defining the extent of testing of specific elements (such as validation, data integrity)? What does it mean "to determine the extent of validation through risk management"? Does it mean the number of test cases or the depth of the test?

Using elements of risk management, validation measures such as design specifications, extent and depth of testing as well as type and frequency of tests/reviews after putting into operation (periodic evaluation) etc. can be determined precisely.

Chapter 2 – Personnel

Speakers:

Klaus Eichmüller, Local Administration of Upper Bavaria (Regierung von Oberbayern)

Dr Jörg Schwamberger, Merck KGaA

Annex 11: "There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties."

What should be understood by "close cooperation between all relevant personnel ..."? What formal requirements should be observed?

No defined formal requirements exist for close co-operation between all relevant personnel during validation. But efforts must be made to ensure that a corresponding division of roles and tasks between the relevant personnel is clearly defined and implemented, including IT.

What training is expected of the relevant personnel?

Requirements concerning training result from the relevant operational provisions on validation. This means that the relevant personnel should know the main regulations concerning their tasks and be able to demonstrate the internally required qualifications to perform the tasks in question. This already arises from the general GMP requirements over and above Annex 11.

Is a formal qualification required (such as ITIL training or something similar)?

Annex 11 contains no further formal requirements concerning personnel qualification other than that resulting from the operational context (see answer above).

What role has a QP to play in validation?

The QP does not have to play a formal role in validation. But inclusion of a QP is recommended as it is the task of the QP to finally release the manufactured product. This release can only be authorised knowing the quality systems used for the proper validation.

Does the QP substitute QA in validation?

The exact responsibilities need to be laid down in the operation procedures. Annex 11 proposes a division into roles that may, however, be independent of a QP and/or QA. Thus the role of the QA has to be defined internally and independently of the function of a QP.

Chapter 3 – Suppliers and Service Providers

Speakers:

Klaus Eichmüller, Local Administration of Upper Bavaria (Regierung von Oberbayern)
Dr Jörg Schwamberger, Merck KGaA

Annex 11:

"3.1 When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service or for data processing, formal agreements must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party. IT-departments should be considered analogous.

3.2 The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.

3.3 Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.

3.4 Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request."

Why do inspectors want to see the supplier's audit reports? Doesn't this contradict the confidentiality agreements with the suppliers?

Without the opportunity to inspect the activities concerning qualification of suppliers, inspectors may not be able to fully evaluate whether due care was applied. In principle, confidentiality agreements are legally subordinated to the relevant legislative provision. Nevertheless, it is recommended that the confidentiality agreements are adjusted accordingly. Apart from that, inspectors are bound by an obligation of secrecy ex officio.

Which points should be taken into account from the inspectors' point of view when evaluating suppliers?

When evaluating suppliers it has to be ensured in general that the supplier's suitability for the task to which he is to be entrusted, is evaluated as well as his ability to accept responsibility for this task.

Are there requirements concerning the auditing of sub-suppliers?

Sub-suppliers (= external suppliers, sub-contractors) must not be audited separately by the contractor if it can be ensured that the principle supplier has laid down regulations ensuring the quality of his suppliers and that these regulations are demonstrably used. The relevant revisions must be documented. The contractor's evaluation should include the ability of the supplier to evaluate the suppliers on his part.

What demands on user requirements are put on COTS (commercial off the shelf) products?

Insofar as COTS products are used for GMP-regulated tasks, their suitability must be demonstrated accordingly within the context of validation. In doing so, the user requirement should define the intended purpose in the company.

What formal requirements exist concerning the choice of a supplier? Must the choice be documented and justified?

The choice of a supplier must be documented and his suitability demonstrated by means of compliance with the pre-requisites in the user requirements.

Does the external supplier/internal IT have to have his/its own QMS? If so, what requirements does this QMS need to fulfil?

If it is ensured that the external supplier/internal IT works according to the customer's regulations, the external supplier does not need his own QMS. It is recommended that this is possibly laid out in a contract and supported among other things by way of respective training. Otherwise the supplier is obliged to maintain a QMS that is demonstrably suitable for his activities.

Chapter 4 – Validation

Speakers:

Dr Arno Terhechte, Regional Government of Münster (Bezirksregierung von Münster)
Eberhard Kwiatkowski, Bayer HealthCare

Annex 11:

"4.1 The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.

4.2 Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process.

4.3 An up to date listing of all relevant systems and their GMP functionality (inventory) should be available.

For critical systems an up to date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.

4.4 User Requirements Specifications should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. User requirements should be traceable throughout the life-cycle.

4.5 The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.

4.6 For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.

4.7 Evidence of appropriate test methods and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy.

4.8 If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process."

What is the definition of "relevant systems"?

Inventory: Relevant / Substantial systems are systems used in order to implement or assist GMP requirements. These systems can be identified within the context of a risk analysis (also supported by a questionnaire).

Is there a definition for "critical"?

No, but Annex 11, chapter 1 gives an indication. Critical systems are systems that directly or indirectly influence patient safety, product quality and data integrity.

How exact must GMP functionalities be described in the inventory?

Only relevant to GMP – yes/no. In the inventory, a description of the general functions is sufficient, i.e. archiving of data, parts list management etc. Detailed information can be found in the system description.

In what way can the URS be created on the basis of a risk analysis if the risk analysis requires an URS as a pre-requisite?

URS and risk analysis are two elements within the context of validation of computerised systems which are closely linked with each other. Requirements can result from a risk analysis but on the other hand it is possible to reach functional solutions on the basis of user requirements on the assessment of risks.

Data flows – does this also mean intersystem interfaces (for example, the interfaces between different modules in ERP- systems)?

Every intersystem interface should be described, including any relevant changes of data format.

Must all user requirements be traceable or only the ones classified as being GMP-relevant?

User requirements, especially those classified as being GxP-critical should be traceable in order to evaluate whether the computerised system is fit for the respective purpose.

What levels of control are expected when using automated test tools?

The level of control results from the criticality of the systems tested and the type of test tools used. A complete validation is not generally expected.

What should test scripts and test results look like in order to be accepted by the inspectors?

Test scripts should contain a specification (expected result) and a description (test performance). The test result should indicate whether the specifications are fulfilled. Failed tests must be evaluated.

Chapter 5 – Data

Speakers:

Karl-Heinz Menges, Regierungspräsidium Darmstadt (Regional Council, Darmstadt)

Sieghard Wagner, Chemengineering Business Design

Annex 11: "Computerised systems exchanging data electronically with other systems should include appropriate built-in checks for the correct and secure entry and processing of data, in order to minimize the risks."

What control mechanisms (such as MD 5) are expected?

The control mechanisms should be suitable for the relevant process or the relevant system. Those mechanisms are to be chosen that minimise the risk adequately.

Should special data formats (such as XML) be preferred?

No, Annex 11 does not specify any directions concerning the data format.

Why are built-in checks required for electronic interfaces if the interface has been validated?

The question cannot be answered as such. The checks of data built in the interface are tested within the context of validation. Changes in a system can be problematic if they concern data that is transferred via that interface.

Chapter 6 – Accuracy Checks

Speakers:

Karl-Heinz Menges, Regierungspräsidium Darmstadt (Regional Council, Darmstadt)

Sieghard Wagner, Chemengineering Business Design

Annex 11: "For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management. "

To what extent must the erroneous entering of data be checked during validation?

It depends on the criticality of the entry. If the entry of critical data is to be checked not by a second operator but by a validated electronic means, it should be checked during validation whether erroneous entries really are detected.

How do inspectors deal with the risk assessment if a residual risk remains in the review?

ICH Q9 clearly points out that there will always be residual risks. What residual risks are acceptable always depends on their potential influences on patients. Principally the residual risk is not the problem but possibly its level.

Chapter 7 – Data Storage

Speakers:

Karl-Heinz Menges, Regierungspräsidium Darmstadt (Regional Council, Darmstadt)

Sieghard Wagner, Chemengineering Business Design

Annex 11: "7.1 Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.

7.2 Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically."

How often should the readability and accessibility of data be checked?

The period should be defined depending on the risk. Readability should be checked immediately after copying and then depending on the medium used.

What requirements are made concerning physical protection?

Physical protection must be adequate to the risk. Physical protection comprises the protection of data storage devices from unauthorised parties as well as the environmental impacts influencing the respective data storage devices. A DVD should not be put in the sun; but this will be less problematic with a hard disk.

Chapter 8 – Printouts

Speakers:

Karl-Heinz Menges, Regierungspräsidium Darmstadt (Regional Council, Darmstadt)

Sieghard Wagner, Chemengineering Business Design

*Annex 11: "8.1 It should be possible to obtain clear printed copies of electronically stored data.
8.2 For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry."*

Are dedicated printouts demanded or are electronic documents sufficient?

Dedicated printouts.

What is the difference between a clear printed printout and a normal printout?

"Clear printed" means that apart from the values themselves, the units and the respective context can also be seen in the printout.

Chapter 9 – Audit Trails

Speakers:

Dr Christa Färber, Staatliches Gewerbeaufsichtsamt Hannover (State Labour Inspectorate, Hannover)

Frank Behnisch, CSL Behring

Annex 11: "Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed."

What are the essential parts of an audit trail?

An audit trail has to at least record the critical variables/values, indicate the initial value and the changed one, indicate who has changed what and when.

This includes a unique identification of the user, a date and time stamp as well as possibly a comment. What's new pursuant to Annex 11 is the comment on the reason for change. Here it would be possible to restrict the number of parameters to be commented by using risk assessment.

What are the requirements on a regular evaluation of the audit trail?

Regularly would also be every ten years. The period of time must be substantiated by means of the process risk and documented. Example: Part of the periodic review or in the case of a batch release, part of the system's event log, and therefore at every release.

What shall be done in the case of legacy systems without audit trail?

First of all, it must be clarified whether the data can be changed at all (e.g.: electronic recorders or SPS). If not, this should be the reasoning within the risk assessment for the audit trail not being necessary. Define in an SOP that each change has to be documented e.g. in a logbook and verified by a second person.

Is a "paper-based" audit trail also possible?

Not with a new system. If a system is introduced today, it must comply with the requirements of Annex 11. An exemption are legacy systems, though. In the case of legacy systems this can be regulated by an SOP if it has been checked beforehand that there is no other possibility.

What does GMP-relevant data mean?

21 CFR Part 11 describes this very well, stating that this means all data required in preceding regulations (in this case this would be, e.g. the GMP Guide, AMG, AMWHV,...). Here, it means at least that data concerning or possibly influencing the product's reproducibility, identity, purity, labelling, efficiency or security.

Chapter 10 – Change and Configuration Management

Speakers:

Dr Christa Färber, Staatliches Gewerbeaufsichtsamt Hannover (State Labour Inspectorate, Hannover)
Frank Behnisch, CSL Behring

Annex 11: "Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure."

What controls are required in the case of a change of configuration?

This has to be defined system-specifically. Measures need to be defined according to a risk assessment. Here, a distinction can be drawn between configurations that are for intended use and are only documented by means of a logbook (such as infrastructure, virus scanner, ...) and configurations which have to be formally authorised and documented by means of a change control (such as release work flow with electronic signature).

Must changes which are not GMP-relevant also be carried out in a controlled manner?

If the whole system is not GMP-relevant = NO. If the system is GMP-relevant = YES, because in an integrated system it must also be evaluated that there is no negative influence. It can also only be ascertained by means of a "risk assessment" that a standard update or standard patch poses no risk and that it therefore can be registered and performed.

Chapter 11 – Periodic Evaluation

Speakers:

Dr Christa Färber, Staatliches Gewerbeaufsichtsamt Hannover (State Labour Inspectorate, Hannover)
Frank Behnisch, CSL Behring

Annex 11: "Computerised systems should be periodically evaluated to confirm that they remain in a valid state and are compliant with GMP. Such evaluations should include, where appropriate, the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports."

What does periodic mean? What period of times is expected as a minimum, for example?

Periodic in this case means regularly and recurrently. No minimum period of time is defined. It must be substantiated that the period of time is adequate in order to control the process risk.

Can such periodical evaluations be incorporated in the annual report or PQR? Must they be incorporated there?

They can be incorporated in the Annual Product Review, but they need not be. Annotation Behnisch: I would not recommend to generally incorporate them in the Annual Product Review as the periods of time in the Periodic Review can usually be longer than the Annual Product Review since the systems are subject to strict change control and possible deviations in the company are controlled by means of the CAPA process.

Since 30 June 2011 the industry has to implement all requirements of Annex 11 "Computerised Systems" of the EU GMP Guideline. Within the context of the Conference on Computer Validation in Mannheim, Germany, in June 2011, authority representatives and industry experts have answered questions concerning the 17 chapters of Annex 11. Here you will find the questions and answers on some of these chapters. Further Q&As were published in the GMP Journal October/November 2011 and April/May 2012 issues.

Chapter 12 – Security

Speakers:

Karl-Heinz Menges, Regierungspräsidium Darmstadt (Regional Council, Darmstadt)
Siegward Wagner, Chemengineering Business Design

*Annex 11: "12.1 Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas.
12.2 The extent of security controls depends on the criticality of the computerised system.
12.3 Creation, change, and cancellation of access authorisations should be recorded.
12.4 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time."*

Does "Operators" mean the users of the system? If so, what is the difference to the audit trail requirement?

The audit trail targets documents of the record/report type. In the case of instruction-type documents, documentation is expected, for example, on who has entered when what version of an SOP in the electronic document system as valid document or suspended it and when.

The identity of operators of management systems for data and for documents should be recorded. Is this requirement valid for control systems?

It refers primarily to DMS; this requirement is not applicable to control systems.

How often do users have to change their passwords? How often must user profiles be checked?

The frequency of change as well as the frequency of control of user profiles depends on the risk. Annex 11 does not pose any requirements on the frequency of password changes.

Chapter 13 – Incident Management

Speakers:

Dr. Christa Färber, Staatliches Gewerbeaufsichtsamt Hannover (State Labour Inspectorate, Hannover)
Frank Behnisch, CSL Behring

Annex 11: "All incidents, not only system failures and data errors, should be reported and assessed.

The root cause of a critical incident should be identified and should form the basis of corrective and preventive actions."

What exactly does "all incidents" mean? Does it also mean service requests (such as resetting a password)?

It means per definition all incidents. But the company can define what an incident is and what the intended use is. Resetting a password, for instance, can be a regular task of the administration and therefore it is no incident since the system documents resetting via log files. Here, you can limit the incidents.

Are workarounds accepted for preventive actions?

Yes, provided they are described and regulated – for instance, in SOPs.

Chapter 14 – Electronic Signature

Speakers:

Klaus Eichmüller, Regierung von Oberbayern (Government of Upper Bavaria)
Yves Samson, Kereon

*Annex 11: "Electronic records may be signed electronically. Electronic signatures are expected to:
a. have the same impact as hand-written signatures within the boundaries of the company,
b. be permanently linked to their respective record,
c. include the time and date that they were applied."*

Is it intentional that the "meaning" (as in Part 11) is not required in Annex 11?

Eichmüller/Samson: In GxP processes, the meaning of a signature is always part of a signature. For the GMP sector, this is regulated in Chapters 1 and 4 of the EU GMP Guideline. This is the reason why this requirement was not repeated in Annex 11. A repetition of this requirement would have ensured

improved clarity – without causing unnecessary redundancy. But principally, the actual wording is not confusing.

How long must data concerning electronic signatures be kept?

Eichmüller/Samson: What data? The signed data may no longer be separated from the signature. Signature and signed data must be kept for an equal period of time. The retention period to be specified must be defined according to the underlying requirements, such as GxP requirements (other requirements may also be relevant: commercial law, liability law etc.). Data concerning the undersigned has to be kept at least as long as the signed data (data concerning the undersigned is in fact metadata of the signed data). In any case, the user data should be kept as long as the system is operated and as long as the signed data must be kept.

How significant is the requirement of the binding legal force in the internal relationship of the company?

Samson: The legal context differs between the USA and the European Union. The USA is one state and does not have a general law on electronic signatures. The EU is a Union consisting of 27 states, subordinated to European law. But these states are obliged to transpose this subordinated law into specific national legislation. This means that the national provisions on electronic signatures may differ slightly from state to state. Where electronic signatures are concerned, there are two directives valid in the EU: Directive 1999/93/EC on a Community framework for electronic signatures and Directive 2000/31/EC on electronic commerce. In Germany, the signature law is also valid. The sentence: "Electronic signatures are expected to have the same meaning as hand-written signatures in the internal relationship of a company ..." means that external regulations such as the Signature Law are not applicable for GxP-relevant electronic signatures within a regulated pharmaceutical organisation. Eichmüller: Because of the different possibilities of the Member States with regard to regulations on the binding legal force of electronic signatures in external relationships, Annex 11 only describes the binding legal force in the internal relationship.

What does "same impact within the boundaries of the company" mean?

Eichmüller/Samson: As a logical consequence of the information above, GxP-relevant electronic signatures can be recognised as equivalent to hand-written signatures within the regulated pharmaceutical organisation.

Chapter 15 – Batch Release

Speakers:

Klaus Eichmüller, Regierung von Oberbayern (Government of Upper Bavaria)

Yves Samson, Kereon

Annex 11: "When a computerised system is used for recording certification and batch release, the system should allow only Qualified Persons to certify the release of the batches and it should clearly identify and record the person releasing or certifying the batches. This should be performed using an electronic signature."

Is this approach also valid for hybrid systems where the release is paper-based, but the release is recorded in an electronic system?

Eichmüller: The requirement that the relationships of the single documents need to be stated in an unambiguous way in a hybrid system is decisive. If documentation of the release decision is paper-based, Annex 11 is to be applied only with regard to the supporting documents. A mere reproduction of a paper-based release decision in an electronic system implies the application of the requirements of Annex 11 but not the requirement of a further electronic signature.

Is there an electronic release?

Eichmüller: A release is carried out by a human being, in the case of a release according to §16 AMWHV or Annex 16 by the Qualified Person (QP).

Is an automatic release possible in the case of real-time release?

Samson: In order to make that absolutely clear, it has to be noted that the so-called Real Time Release has to be understood as Real Time Release Testing (RTRT). There has never been an intention to carry out batch releases automatically. Rather, and in the sense of ICH Q8, it is possible to replace release-relevant quality controls in the laboratory with real-time testing as long as the process and validation permit such testing.

Eichmüller: It is true that automated aggregations of data are possible by means of validated processes but the release is carried out by people. In terms of RTRT, further possibilities of application can be anticipated for the future (compare EMA's relevant Concept Paper) but I don't see the possibility of an automated release yet. (Annotation: At the end, there also is the question about responsibility and the related liability).

Chapter 16 – Business Continuity

Speakers:

Klaus Eichmüller, Regierung von Oberbayern (Government of Upper Bavaria)

Yves Samson, Kereon

Annex 11: "For the availability of computerised systems supporting critical processes, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system). The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested."

Is a high availability of critical processes required independently of the question as to whether such availability is necessary?

Samson: The availability of a process should be proportionate to the needs. This means that a process which is applied only seldom needs not to have a high availability even if it is a critical process from the GxP point of view. The process should only be available if needed. It has to be noted however that a process which is applied often or continuously might be assessed as being more critical from a business perspective than it is according to GxP.

Eichmüller: Chapter 16 focuses on the criticality of restoring process support. This leaves room for manoeuvre for GxP-critical processes. But the relevant decisions must be substantiated rationally on the basis of risk assessments.

Must the system availability of each single system be tested or is a general test sufficient?

Eichmüller/Samson: First of all the systems requiring higher availability must be identified. The availability of a group of systems can not only be tested "generally". To be efficient and in conformity with the requirements, contingency plans need to be designed system-specifically and sufficiently in

detail. Contingency plans can either be defined as SOP or be accompanied by SOPs. In any case, the contingency plans should be trained and practiced regularly. They must invariably be directed so that plans and measures are reviewed and possibly adapted in the case of hardware or software changes or organisational changes. Furthermore, the co-operation by the emergency measures of the individual systems should be reviewed and trained in the case of complex processes with embedded or interconnected systems.

Chapter 17 – Archiving

Speakers:

Klaus Eichmüller, Regierung von Oberbayern (Government of Upper Bavaria)

Yves Samson, Kereon

Annex 11: "Data may be archived. This data should be checked for accessibility, readability and integrity.

If relevant changes are to be made to the system (e.g. computer equipment or programs), then the ability to retrieve the data should be ensured and tested."

How often should the readability of archived data be checked?

Eichmüller: This is to be defined by the company and depends on a set of further factors (see below) – apart from the type of system or data.

Samson: There is no simple and general answer to this question since the readability of a data storage device depends on various factors; including the technology used, the storage conditions of the data storage devices and the reliability of the requisite disk drives. That is the reason why the period of review should be defined based on the identified risks, the criticality of the data and, if applicable, experience. This point should in any case be a subject of the periodical evaluation.

Is a single test enough to demonstrate the readability of archived data?

Eichmüller: A single test does not at all fulfil the requirement of ensuring readability. The frequency of testing depends on different factors such as the archived process and the software and hardware used (see above and below) and should, for logical reasons, be defined individually. Samson: A single readability test is definitely not enough, since the aging process of the data storage devices and the disk drives used cannot be taken into account in that case. Furthermore, the availability of the requisite hardware and system software can play an important role as regards very old systems. This is the reason why periodic control of readability is indispensable.

3.2. Data Integrity

1. Is it necessary to carry out a Data Integrity Assessment? Which areas must be covered by such an assessment? Does the management need to be involved?

Eberhard Kwiatkowski, PharmAdvantage

The integrity of data must always be verified!

An assessment with pre-defined questions can only be performed for operating systems that have not yet been DI-checked. The assessment should help to recognize the gaps and to take suitable measures. A prioritization of the systems with respect to the period of implementation of the activities has also to be done. At this point, the management comes into play and must provide the necessary resources to be able to carry out the activities.

2. Must data flow diagrams be available?

Karl-Heinz Menges

Annex 11 to the GMP Guidelines requires that a current system description must be available for critical systems, which also reflects the data flow.

The PIC/S document PI 041 mentions data flow diagrams in connection with risk assessment: 5.5.3 Risk assessments should focus on a business process (e.g. production, QC), evaluate data flows and the methods of generating and processing data, and not just consider IT system functionality or complexity.

9.1.5 When determining data vulnerability and risk, it is important that the computerised system is considered in the context of its use within the business process. ... The creation and assessment of a data flow map may be useful in understanding the risks and vulnerabilities of computerised systems, particularly interfaced systems.

If one comes to the conclusion that a data flow diagram is not necessary for a concrete system, the rationale for it should be documented.

3. Do specific training programmes in manufacturing and quality control need to be in place to sensitise employees to the topic of data integrity?

Dr Wolfgang Schumacher

All guidelines on data integrity published in recent years require specific training for personnel; in addition to general information for employees, all persons involved in GMP should receive special intensive training. The topics include both the documents issued by the management on data governance and the detailed regulations (e.g. on the Audit Trail Review) with regard to production and QA/QC.

4. Is it necessary to define which data must be retained in which form and for how long? Does this definition have to be specific to the method or process or is a comprehensive definition expected?

Karl-Heinz Menges

It is essential to determine which data must be retained and for how long in order to comply with legal requirements. The German Medicines Act (AMWHV) specifies in detail how long documents must be retained. If necessary, requirements of other legal areas that go beyond this must also be observed. It is up to the regulated user to decide whether he/she wishes to carry out these specifications across all areas or product-specifically.

5. Are there specifications regarding who and to what extent a data review must be carried out and how the results should be documented?

Eberhard Kwiatkowski, PharmAdvantage

There are no detailed specifications for the data review. It depends on the criticality of the data generated or processed and must be defined by the pharmaceutical manufacturer. This also includes the type of documentation. It makes sense to create checklists. These can be made in electronic form as well as on paper. What is important is that an evaluation is carried out and documented. The Qualified Person is responsible for this.

6. If GMP-relevant data is created and "delivered" by third parties, how does it have to be ensured and verified that the contract manufacturers / contract laboratories / service providers also meet the data integrity requirements (ALCOA+)?

Dr Wolfgang Schumacher

When data is provided by contract manufacturers, contract laboratories or other service providers, the final responsibility always remains with the pharmaceutical manufacturer. The data integrity requirements must be clearly specified in the contract or SLA (Service Level Agreement) for the delimitation of pharmaceutical responsibility. This also includes an information obligation on the part of the contractor, who must inform the customer immediately of the discovery of a data integrity issue (e.g. within one day).

7. Must there be regulations for remote access by service providers to GxP-critical systems? What data integrity requirements must be included?

Dr Arno Terhechte, Bezirksregierung Münster (District Government of Münster)

Remote access enables service providers to access computerised systems via a network connection aiming at troubleshooting or changing the configuration. Where a GxP critical computerised system is accessed remotely, the activities of the service provider or service company may alter the system so that it no longer remains validated. Therefore, remote access and actions performed during this session should be controlled and documented. This means that the access should be actively enabled by the RU (regulated user) and that it should take place via a secure network connection. Besides, it should be noted which activities were carried out within the scope of the access. If necessary, a

change control process should be initiated. The aim is to maintain and control the validated state of the system.

8. What agreements need to be included in contracts with cloud service providers in order to ensure data integrity?

Dr Arno Terhechte; Bezirksregierung Münster (District Government of Münster)

The introduction of cloud services into the GMP environment increases. The cost factor dominates the discussion; however, specific risks need to be taken into consideration. Especially the issue of data integrity in cloud applications is not to be underestimated. What agreements need to be included in contracts with cloud service providers in order to ensure data integrity?

The necessity for contractual agreements is laid down in chapter 7 "Outsourced Activities" of the EU GMP Guidelines as well as in Annex 11 "Computerized Systems" of the guidance. The following are requirements for contractual agreements between a Regulated User (RU) and a Cloud Service Provider (CSP) which are meant to ensure the integrity of data (in motion and at rest). These requirements cannot explicitly be found in the EU GMP Guidelines, they should however be considered as useful:

- Data transfer should only occur in encrypted form and in a way which ensures that the data being transferred are complete and unchanged.
- CSP handling sensitive data or data with high availability requirements must have a certified ISMS (Information Security Management System) in place (e.g. as per DIN 27001).
- CSP handling sensitive data or data with high criticality must submit to penetration testing in the course of their qualification.
- Sensitive or critical data may only be stored in encrypted (or pseudonymized) form.
- A deployment model should be chosen based on criticality. Private or community cloud models should be chosen rather than a public cloud for sensitive data.
- Sharing data with a third party (e.g. subcontractors), e.g. providing infrastructure (storage space for backups, redundant computing power, etc) should be prohibited or dependent on the RU's approval.
- The deletion of data must be fully guaranteed.
- It must be possible to export data in a way that allows RUs to switch CSPs or get the data back on premise.
- Only a limited, specifically selected and qualified group of people from the CSP should be able to access the data.
- If data has been encrypted, the key management should lie with the RU.
- The CSP informs the RU about changes which might impact the application or database. A notification of change with release note is expected, ideally issued before the actual implementation of the change so that the RU may check the effects of those changes, if necessary.

9. Which regulations are necessary as to how the data is completely returned to the client in the event of the closure (insolvency) of a cloud service provider (CSP)?

Dr Arno Terhechte, Bezirksregierung Münster (District Government of Münster)

Both the German Act (AMWHV) and the EU GMP Guidelines see the responsibility in the RU. The AMWHV focuses on the retention of documentation, i.e. the availability of GxP-critical data. According to § 20 AMWHV, in the event of closure of the manufacturing or testing facility in which the documentation is stored in accordance with clause 1, the pharmaceutical company must take provisions to ensure that the documentation is retained for the entire storage period.

The EU GMP Guide focuses on the business process and thus on the GxP-critical application and the data. According to Annex 11 to the EU GMP Guidelines, Chapter 16 Business Continuity, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system), when computerised systems support critical processes. The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested.

This task / obligation could be included in the service contract with the CSP by obliging the CSP to ensure the availability of data and, where appropriate, application through an additional subcontractor.

However, the RU should evaluate in a risk assessment whether it would not make sense to maintain a backup site on premise.

10. Do existing QA systems need to be checked for adequacy of the rules to ensure data integrity in electronic and paper-based systems? What points need to be particularly taken into account here?

Dr Thierry Dietrich

Not only the WHO, but also the EMA, the FDA, the MHRA and the PIC/S expect regular or even continuous monitoring of the effectiveness of established procedures aimed at ensuring data integrity (self-inspections, internal audits, etc.). Preventive measures must be taken if weak points are identified in the quality management system that could lead to data integrity incidents (preventive actions).

For concrete data integrity incidents, established procedures must be followed in order to investigate them appropriately and to ensure that they cannot occur again in the future (deviations/NC/corrective actions).

These aren't surprising requirements but absolutely consequential ones. The data management system to ensure (among other things) data integrity should be an integral part of the quality management system. For the latter, the requirements above apply and thus also apply implicitly to its components. For both aspects, established quality management systems should therefore already include suitable procedures.

The data integrity analyses or related risk analyses which are also expected by the WHO, the EMA, the FDA, the MHRA and the PIC/S reveal which items should be given special attention. If a new data management system is introduced, tools such as gap analysis could help to identify any gaps or weaknesses in the quality management system with regard to data management.

11. Do all worksheets, production records, test records etc. have to be uniquely identified? How must the issue and the return of worksheets be checked?

Karl-Heinz Menges

Chapter 4 of the EU GMP Guidelines requires the following: "*documents should ... be uniquely identifiable.*"

This requirement is interpreted by some authors to mean that each piece of paper in a pharmaceutical company must be given an individual number but it is ignored that requirements for instruction documents are laid down in EU GMP Chapter 4 section „4.3 Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.“

12. How must it be ensured for electronic systems that employees can only carry out actions that correspond to their specific tasks (need to know, need to have)?

Frank Behnisch, CSL Behring

Annex 11, § 12 describes this very clearly: " Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas. The extent of security controls depends on the criticality of the computerised system. Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time." There is little to add. In practice, this means a concept of role and rights that is oriented to the requirements of the supported process. For example, it can be guaranteed that the operator may only carry out the steps described in the SOP he or she has also been trained for or which correspond to his/her level of training and his/her function in the company.

13. How do risks to modify or delete GxP-critical electronic data (unintentionally or intentionally) need to be addressed in the risk analysis of computerised systems?

Thierry Dietrich

Data integrity requirements must be considered in risk analyses according to the WHO, the EMA, the FDA, the MHRA and the PIC/S. It is up to the responsible party whether this is done in a so-called "risk analysis of computerised systems", in a specific data integrity risk analysis or other risk analyses. There are also no specific requirements as to how such risks should be addressed. This is also not possible because the individual uses of computerised systems will differ greatly from one another even within a single company. In a computerised system, which is mainly used to produce electronic GxP documentation, it could be possible and useful to completely prevent the modification or deletion of entries made, if these are recorded electronically (e.g. if a temperature sensor passes a measured value directly on to the recording system). In the case of manual recording, this may be undesirable. A risk analysis should identify and analyse risks specific to the process and computer system for critical GxP data and, if necessary, define appropriate specific countermeasures.

14. Do data need to be stored in the native format or converted to an application-independent format?

Wolfgang Schumacher

Dynamic data must be stored in the native data format to enable reprocessing. Static data needn't to be stored; the printout is sufficient.

15. Does the deletion of data have to be regulated in a SOP?

Klaus Feuerhelm Regierungspräsidium Tübingen

Deleting GMP-relevant data is considered critical. The deletion of GMP-relevant data in a computerised system must be recorded by an audit trail. Annex 11 of the EU-GMP Guidelines states:

"12.4 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time."

Basically, it must be possible to recognize who is deleting data within such systems. Deleting data endangers data integrity and is a critical step. Work steps must be described in standard operating procedures (SOPs):

Chapter 4 of the EU-GMP Guidelines - Required GMP Documentation:

"Procedures: (Otherwise known as Standard Operating Procedures, or SOPs), give directions for performing certain operations."

Deleting data that is no longer required is allowed. Deletion is the last step in the data life cycle. Safe procedures must be established for the deletion of GMP data.

Data should normally only be deleted after the end of their retention period. There are very few exceptions as to when data may be deleted before the end of its retention period. This includes, for example, data that has been migrated to another system. The deletion of data must be described in detail in a relevant SOP.

Is it necessary to harden computerised systems to prevent accidental changes to data and metadata?

Thierry Dietrich

Although this would be an ideal objective, it will certainly not be possible in all cases.

This should be achieved where the intended use and the technology employed in a computerised system allow for the total prohibition of changes to critical data and metadata.

However, it is also possible that:

- the intended use of the system does not permit this,
- the system cannot detect whether a change is intended or unintended; or
- this is technically not feasible.

In these cases, a risk analysis should be carried out to examine whether and which alternative control measures should be taken to bring the risk to an acceptable level.

16. How to ensure data integrity when transferring data from one computer system to another (data in motion)?

Wolfgang Schumacher

The best way for data transfer between systems is a direct interface without intermediate storage. If this is not possible, or if the data is transferred via the Internet or an unsecured data connection, for example, the data should be encrypted.

17. Does a training programme on data integrity need to be established in a company? What must be included in this training programme?

Dr Wolfgang Schumacher

The topic of data integrity must be integrated into the routine training programme of pharmaceutical companies. All employees working in GMP must be trained in the details of data integrity. This includes in particular those processes in which employees have forgotten entries in protocols, for example, which must be later performed out in compliance with GMP. A training programme should also draw attention to the consequences of knowingly making false entries (falsifications) for the employee (warning, dismissal).

18. What must be addressed regarding data integrity in the auditing of contract manufacturers? Is a standard operating procedure necessary for this?

Wolfgang Schumacher

An appropriate paragraph shall be included in the delimitation agreement to ensure data integrity. In this paragraph, the contractor shall be obliged to inform the client immediately in the event of DI issues. Furthermore, the audit should verify whether third parties (e.g. cloud service providers) have been commissioned to store data. If external manufacturers or testing laboratories are used for the manufacture or testing of the products, the secure transmission of the batch records, for example, is very important: the e-mail system must NOT be used for this purpose. The topic of data integrity should be included in the SOP "Auditing of contract manufacturers", together with corresponding audit questions.

19. Must there be a concept for evaluating the criticality of data? And what rules for entering critical data into computerised systems must be available?

Klaus Feuerhelm, Regierungspräsidium Tübingen

The evaluation of data with regard to criticality is essential and - to some extent - no trivial activity. Data must be evaluated in particular with regard to patient safety and/or product quality.

The term "critical data" appears at only one place in the EU GMP Guidelines:

"4.27 - A system should be in place to indicate special observations and any changes to critical data."

The EU GMP Annex 11 also mentions critical data at only one place.

"6. Accuracy Checks - For critical data entered manually, there should be an additional check on the accuracy of the data."

This provides a legal basis for reviewing the entry of critical data. A second person must therefore verify it. An alternative would be a validated computerised system.

Example:

The temperature is measured in a stirring tank. This measurement is part of the batch report and is relevant for release. The temperature is read manually and documented manually. In this case, a second person is required to check the correctness of the data (double-checking principle).

or

The temperature is recorded electronically via a computerised system and saved electronically. In this case, the computerised system would have to be validated.

Back to the evaluation of data criticality: neither section 4.27 nor Annex 11 (section 6) provides much information about which data is critical and which is not. There is no legal definition of critical data in the GMP environment. If one looks at the various guidelines and standards in the GMP area, a definition for critical data can be found in VDI/VDE 3516 Part 5 on "Validation in the GxP environment - Types of raw data":

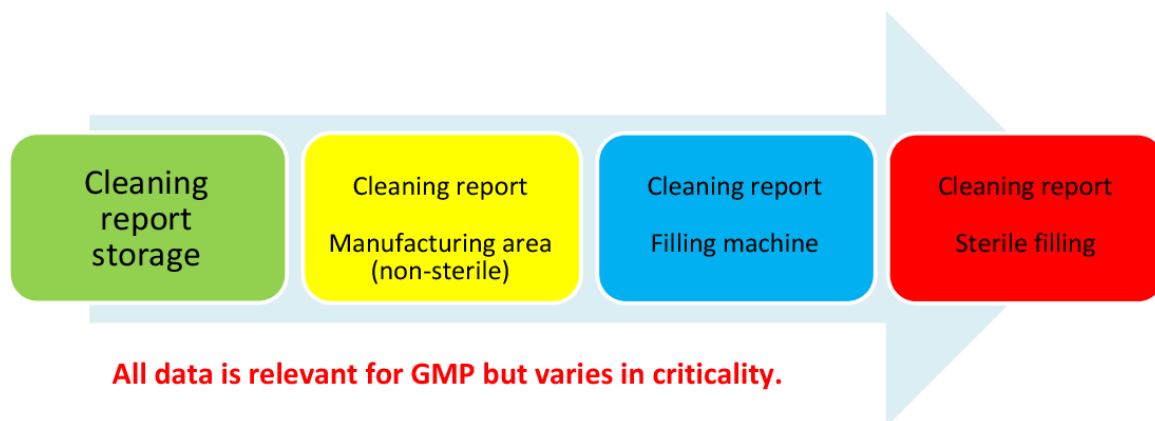
"Critical data:

Data that has a potential impact on patient safety, product quality and data integrity".

It is the decision of the company (medicinal products manufacturer) to define the data to be included.

The crucial question is certainly: Is there any GMP-relevant data which is not critical?

This cannot be answered unequivocally from the contents of the current legal bases. However, the answer "No" is the productive one. Yet, there are differences in the criticality of data. Figure 1 shows a corresponding example. A three-level classification makes sense:



Criticality is high, medium or low.

PI 041 GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS provides information on critical data, which also proves their significance.

Example:

"5.4 Data criticality - For example: for an oral tablet, API assay data is of generally greater impact to product quality and safety than tablet friability data".

The document stresses the importance of data in terms of its influence on decisions such as the batch release.

"5.4 Data criticality

5.4.1 The decision that data influences may differ in importance and the impact of the data to a decision may also vary. Points to consider regarding data criticality include:

Which decision does the data influence?

For example: when making a batch release decision, data which determines compliance with critical quality attributes is normally of greater importance than warehouse cleaning records"

20. Are regulations necessary for the handling and management of data generated by small systems (e.g. pH meters, filter integrity testers, etc.)?

Klaus Feuerhelm, Regierungspräsidium Tübingen

As a rule, GMP-relevant data must be documented. It doesn't matter if this data is generated by large or small systems. Basically, the handling of this data must be regulated.

GMP-relevant data from small computerised systems may have to be read directly from the device and written down by hand. If the system has a printer interface, this interface should also be used. This is an essential step to ensure data integrity.

This also means that when purchasing such small systems, one should already make sure that they have a printer interface. The printer ensures an independent and correct recording of the data when the system is qualified. Raw data is demonstrably available:

MHRA 'GxP' Data Integrity Guidance und Definitions from March 2018:

6.2 "In the case of basic electronic equipment that does not store electronic data, or provides only a printed data output (e.g. balances or pH meters), then the printout constitutes the raw data."

Especially with small systems, it is possible to manipulate data. Restrictive requirements for the handling and documentation of such data are mandatory.

The MHRA 'GXP' Data Integrity Guidance and Definitions document from March 2018, for example, refers to this risk:

4.3 "Within these systems, it may be possible to manipulate data or repeat testing to achieve the desired outcome with limited opportunity for detection (e.g. stand-alone systems with a user-configurable output such as ECG machines, FTIR, UV spectrophotometers)."

21. Do administrator rights have to be separated from the business process user, including master data management (workflow, critical parameters, etc.)?

Dr Wolfgang Schumacher

Administrators usually have extensive rights for the systems they manage; they can add, change or delete GMP-relevant data. It must be ensured that the administrator doesn't influence such data. This is best done by clearly assigning the GMP activities in the user or administrator profiles. In the production area, critical machine parameters should be set to the specified target values (according to the specifications) by a function independent from the operator (e.g. engineering). This ensures that the operator can only make limited changes to the settings within the approved "Design Space".

22. Does the system need to protect the data by preventing deletions by the operator?

Frank Behnisch, CSL Behring

Deletions by the operator are not categorically excluded. This must be defined in accordance with the process requirements and evaluated on the basis of the risk. At least, however, an audit trail must be established that records the deletions including the audit trail data (who, when, deleted or changed from what to what and why). Data can be deleted at the end of the retention period.

Depending on the process security requirements, it may be advisable to protect the deletion of data with rights.

23. Do all users have to log in using unique user IDs?

Frank Behnisch, CSL Behring

Yes. This is laid down in Annex 11, §12 as well as in the US-American 21CFR Part 11. A group password is not acceptable.

24. How do I practically proceed if I want to recognize the state of DI in the company? How do I document it?

Dr Wolfgang Schumacher

The status of implementation of a data integrity concept in the company can best be determined by means of a gap analysis. The policies issued by the company management (DI Policy, DI SOP) and the evaluation of the implemented computerised systems in production and quality control are checked. These include in particular the so-called "Segregation of Duties" and the regular review of

the audit trails in the quality-relevant systems. The gap analysis should be regularly reviewed and updated. It is used during an official inspection to prove the current DI status.

25. What influence does IT technology have on data integrity (e.g. Active Directory, DNS, Citrix, Windows systems, authorization concepts)?

Thierry Dietrich

This is a very complex and broad question.

Basically, it can be stated that IT:

- brings with it new data integrity risks that did not exist in the obsolete paper process.
- enables technical risk control measures that help reduce or better control data integrity risks that were previously unavailable in paper-based processes.

Thus, the IT used can have both positive and negative effects on data integrity. In addition to the inherent risks and opportunities compared to paper-based systems, the implemented IT design can also have a positive or negative impact on data integrity. Different software and hardware architectures can have distinct risks with regard to data integrity.

Examples of technologies have already been listed in the question. MS Active Directory (properly implemented) can help to securely manage identities, secure access to GxP applications, secure access to GxP data, and identify users more securely in the event of data changes (audit trail) or electronic signatures. However, there are other products on the market for this purpose. Such technologies are highly relevant to data integrity.

Citrix architectures (correctly implemented) can also improve the control of data integrity risks, as access to the application and to the data can be technically more restrictive. The technical implementation and the intended use of the application are very important here.

Authorisation concepts become more and more important with the increasing complexity of a computerised system (number of users, number of roles, number of functionalities, etc.). The existence or non-existence of a professional authorisation management system within a computerised system and its functional scope can therefore have a considerable influence on data integrity.

26. What are the implications of updates, patches, hotfixes, etc. for data integrity in the regulated area? What do I have to do when installing?

Frank Behnisch, CSL Behring

Patches, hotfixes and updates are also changes. As such, they must also be handled according to the company's change control procedures. At least an evaluation of the possible effects on the validated system is required. Based on this, appropriate measures up to change validation with regression testing may have to be defined. In the best case scenario, the risk assessment ensures that there is a high probability that no undesirable effects on the application can be expected (e.g. in the case of simple infrastructure measures such as the update of switches) and that further measures are not required.

27. How can I handle analysis devices that are connected to a LIMS via a middleware? The manufacturer does not allow access to the original data in the automated analyser though.

Eberhard Kwiatkowski, PharmAdvantage

This question considers raw data to be the same as generating the first data. This is not recommended. In the GMP environment, the raw data should be defined by the pharmaceutical manufacturer. The type of data generated is important for defining it. Is static data or dynamic data available? If the data is static, the raw data can consist of cumulative primary data (first generated data). In the case of dynamic data, raw data can be the original data.

The following definitions are necessary for answering this question:

Original Data:

This represents the first recording of the data which is kept in the first storage location (e.g. analogue data).

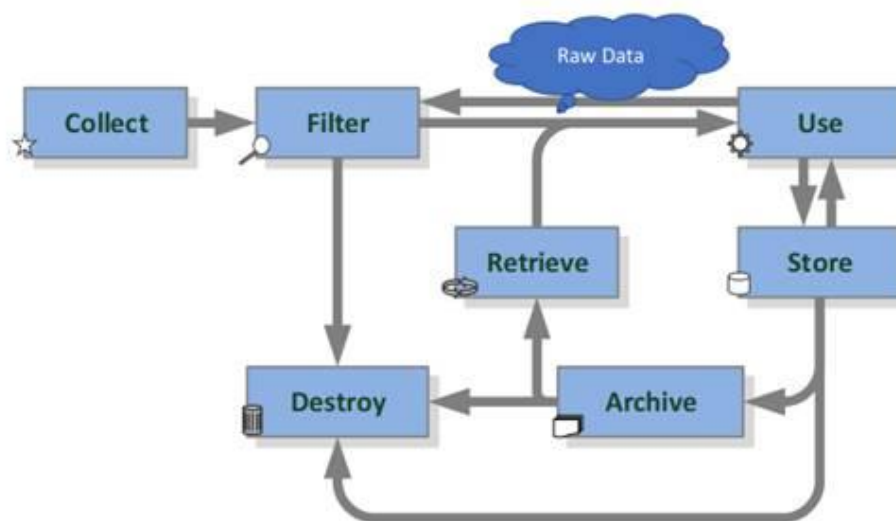
Primary Data:

This is processed data that leads to the result on the respective device. If this data is collected on the device of origin, it can also be considered as original data (e.g. digital data calculated from an analogue signal).

Raw Data:

This is the specified data (from the totality of all available data) necessary for the reconstruction and evaluation of the derived outcome data relevant to patient safety, study results and/or product quality.

The data life cycle (see figure below) shows that raw data can be defined by the evaluation.



Once the output data which is definitely required has been defined, the second step is to determine which input data (e.g. individual values) is necessary on the basis of the available data processing methods and which processing methods are needed for this.

In addition to the definition of the data types, it is also important to determine whether all individual values are required as raw data in order to be able to reproduce the result. If traceability is no longer possible because the generated data is not available in the LIMS, this process is not "compliant". In this case at best, validation can provide help: it must be proven that all relevant (to be defined) data is transferred to the LIMS in order to check the plausibility (traceability) of the result.

28. Do the analytical data count as critical data in the course of validation of analytical procedures?

Thierry Dietrich

First of all, data can only be as critical as the process itself that generates it. If a process is not critical in itself, the data is not.

In a critical analytical procedure where its result has a direct influence on the release of a batch for example, the corresponding result data is - of course - also critical.

The data generated during the validation of a procedure is essential for the documented evidence of the suitability of the analytical procedure. If this data is missing or if it is not of integrity, the suitability of a critical analytical procedure cannot be systematically proven. Thus, even all (critical) individual results from this procedure would no longer be trustworthy, i.e. no longer of integrity. In this respect, the validation data of a critical analytical procedure can also be considered critical.

29. Is it necessary to retain and archive all electronic data during a sterile process or is the batch record sufficient?

Thierry Dietrich

Archiving is merely a long-term storage method (among others) with slower access times. This applies to both paper and electronic records (which in turn contain data). There is no archiving obligation. However, there are requirements for retention periods with different times depending on the type of recording as well as requirements for access times (e.g. as part of an inspection).

A batch record can be paper-based, electronic or hybrid (paper-based and electronic). The above question seems to relate to cases where the data required to generate the batch record originates from an electronic "source system" (e.g. a LIMS, MES or ERP system) and it seems to be the question whether the data concerned must be stored electronically in addition to the batch record in the source system or in some other way.

The FDA writes in its guideline for data integrity published in the middle of December 2018 that a transfer of "cGMP records" which were available in their original form as "dynamic data", into a paper or "static" copy did not satisfy the requirement of §211.180(d). Such copies did not represent original records or true copies in the sense of the law and could, for example, not be re-processed and possibly be incomplete.

The MHRA also demands in its final guideline on data integrity dated March 2018 that data should be kept in a dynamic form if this is necessary to maintain their integrity or for later verification. The PIC/S demands this analogously in the 3rd draft of the guideline PI041-1 of November 2018 and the WHO in its draft guideline of September 2015, if the dynamic nature of electronic data is important for the content and significance of a recording.

Audit Trail

1. Changes and deletions of GxP-critical data must be tracked via an audit trail. What measures must be taken if the systems do not have this functionality?

Karl-Heinz Menges

If a system does not have an audit trail functionality, it should first be checked whether data can either be blocked or restricted to a specific group of users by means of appropriate rights, changes, and deletions. There must be a SOP which specifies how changes and deletions must be documented by these users and who must be informed about the activity and how. These should be at least those persons who make decisions about the quality of a product or material based on the changed data.

2. Is the Audit Trail review required by the authorities before each batch release, or is it only recommended?

Klaus Feuerhelm, Regierungspräsidium Tübingen

The requirements for the Audit Trail and its review are formulated in Annex 11 of the EU GMP Guidelines: 9 Audit Trails: "*Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed*". The reason for the change or deletion of GMP-relevant data should be documented. Audit Trails must be available, convertible into a generally readable form and regularly reviewed.

If one first looks at the information provided by the legal basis of EU-GMP Annex 11 Section 9 Audit Trails, there are no concrete instructions as to when an Audit Trail is to be reviewed. Here, you can only find the specification concerning the regular examination:

"Audit Trails must be available, convertible into a generally readable form and checked regularly".

The EU GMP Annex 11 Section 8 "Printouts" is much more concrete:

"8.2 – For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry."

Conclusion:

This clearly addresses the documentation related to lot release and involves modified data. This can only mean that an Audit Trail check of the data to be seen in connection with the batch release must also be checked before the release.

Although the PIC/S document PI 041 GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS doesn't constitute a legal basis, it can be assumed that inspectors worldwide will follow the provisions and requirements of this guidance. Here, it is again confirmed that all Audit Trails to be seen in connection with batch release must also be reviewed before release:

"9.4 Audit trails for computerised systems: Critical audit trails related to each operation should be independently reviewed with all other records related to the operation and prior to the review of the completion of the operation, e.g. prior to batch release, so as to ensure that critical data and changes to it are acceptable."

3. What can be done if an audit trail upgrade is not possible for a hybrid system?

Karl-Heinz Menges

Procedural measures must be taken to ensure that changes to GMP-relevant data are documented in accordance with the rules of Good Documentation Practice. The company should have a measures action plan which specifies the sequence in which systems without an audit trail are to be replaced. This should be based on a documented risk analysis.

4. May the laboratory manager have administrator rights, e.g. to perform the audit trail review?

Eberhard Kwiatkowski, PharmAdvantage

Here, reference should be made to the conflict of interest. Anyone, including the laboratory manager, who generates, processes and/or releases data may not be an administrator!

The report for the audit trail can be generated by the administrator. However, this report is not operationally active for this system.

5. How to handle old devices if there is no audit trail available or a "user login" is not possible?

Klaus Feuerhelm, Regierungspräsidium Tübingen

First of all, it is clear from the contents of the Annex 11 to the EU GMP Guide that an audit trail should be available in connection with GMP-relevant data and their modification in a computerised system. If this functionality had not been available at the time the system was acquired, it should first be checked whether an update with the audit trail functionality is now available for the system. If this is not the case, a corresponding alternative should be provided. EU GMP Annex 11 does not describe what this alternative should look like.

One possibility would be to use handwritten audit trail logbooks. This alternative is also suggested by the PIC/S in the document PI 041 GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS:

9.4 Audit trails for computerised systems:

If no electronic audit trail system exists a paper based record to demonstrate changes to data may be acceptable until a fully audit trailed (integrated system or independent audit software using a validated interface) system becomes available. These hybrid systems are permitted, where they achieve equivalence to integrated audit trail, such as described in Annex 11 of the PIC/S GMP Guide.

6. Devices/equipment often have standard audit trail functions. A lot of data is recorded (on/off) and only a small fraction is critical and relevant for reviews. What is the best way to proceed with?

Frank Behnisch, CSL Behring

The perception has changed especially with regard to the audit trail. Before the revision of the Annex 11, the general point of view was the preservation of evidence in order to have further data available

in case of a deviation. Also statements of the American authority (FDA) nourished this point of view: in their Dockets it is stated: "Audit Trail... we may use it for a useful purpose e.g prosecution". As a result, the focus in the software was not on later evaluability, but on recording. Therefore, the audit trail data was simply stored sequentially in tables. So far, there are only a few systems that fully support the new requirements. Now, with the additional demand, also including the reason for the change, there are further demands on the systems and also further sorting criteria. In addition, it was clarified that the audit trail can be limited according to a risk-based procedure. Here, the opportunity lies in the limitation to the essential data. Both Annex 11 §9 as well as Chapter 4 of the EU GMP Guidelines describe what these are. Further information can be found in the "Aide Memoire" (Aide-mémoire 07121202) published in the ZLG, where the following quotation can be found: "1 - Based on a risk assessment, consideration should be given to integrating the recording of all GMP-relevant changes and deletions into the system (a system-generated "audit trail"). 2 - When changing or deleting GMP relevant data, the reason should be documented. 3 - Audit trails must be available, be legible and regularly reviewed.". Therefore, it makes sense to first derive the definition of the relevant data for the audit trail from the definition of the raw data, in order to then determine for which data a review must be performed and which assessment criteria must be applied. This is in line with the requirements laid down in Chapter 4, where it is stated that at least the data on which a quality decision is based must be designated as raw data.

Since usually the data itself is not changeable with the controls (SPS) and process control systems, one might also argue if necessary that no audit trail is carried out, because the data is not changeable. However, this argumentation must be proven by appropriate validation with the evidence of the raw data protected by proprietary formats or strong access protection. This means that there must be test cases that prove that this defined raw data cannot be changed accidentally or with simple effort.

For such systems that do not have an audit trail, the Aide Mémoire mentioned above points out that in exceptional cases, in the case of legacy systems without an audit trail, an SOP can be used, for example, to document the corresponding change in a logbook and have it verified by a second person. It should be noted here that only those systems are defined as legacy systems which were installed before Annex 11 (1992) came into force (see Aide-mémoire 07121202, page 28, serial no. 2.4.5.9). There is also the sentence: "First it has to be clarified whether data can be changed at all (e.g. electronic recorders). If no, no audit trail is required."

For systems where there is a simple audit trail, a report tool should be used to query based on the definition of the raw data. At least those entries should be displayed that belong to process values that are required for a quality decision. If the data, e.g. temperatures, are directly related to the batch release, it should be checked whether the associated audit trail must also be evaluated before the batch release. For systems that also record the reason for the change, groups can be sorted by reason and clusters can be recorded and evaluated by reason. The evaluation should always be prioritized according to the risk for the product and thus for the patient. In second instance then also accumulations of reasons can offer reason to question technical defects.

The laws and guidelines themselves do not allow the requirement for a technical audit trail to be deduced, which virtually covers all configurations with basic data and records them in the audit trail. There is a change control procedure for these processes. As a result, no reviews of this data are expected at this point.

It should be noted here that the guidelines always assume that values will be changed and that the initial entry will therefore only record who has entered it in the sense of a hand signal for paper documents. This distinction is very well described in Votum V11003. In section B, penultimate paragraph, it says: "Automatic logs of the user are suitable to replace a hand signal".

In order to meet the requirements of the audit trail review, further technical functions will be required in the future, such as configurable selection menus which allow selecting the reason for the change and providing standard reports and at least descriptive statistics.

7. Which person, e.g. in the laboratory, should perform the ATR?

Dr Wolfgang Schumacher

There are contradictory statements in the literature about the responsibility for conducting the audit trail review: While the current guidelines from the WHO, MHRA and PIC/S see the responsibility for the review in the department that generated the data, the FDA (in the final version of the guideline published in 2018) requires a review by the Quality Unit, i.e. quality assurance. Experts from industry and European authorities consider the FDA approach to be rather inappropriate, as the QA cannot

ensure full detailed knowledge of all production and quality control processes. This applies especially to biotechnological processes.

8. Many production processes are documented on paper by means of manufacturing protocols. How does a review of the audit trail stand in relation to this? Should the good documentation practice in the manufacturing protocol be checked by means of an audit trail review?

Karl-Heinz Menges

If the documentation is done electronically, it is not clear in many cases whether a specific value is the original entry or whether changes have been made subsequently and how the changes were justified. In paper-based (manufacturing or test) records, changes must be made in such a way that the original entry remains legible and the change must be signed and dated; if this is not obvious, the reason for the change must be stated. (EU GMP Guidelines Chapter 4 No. 4.9) This allows the person who decides on the quality of a product or material to see whether subsequent changes exist and evaluate them. In the case of electronic documentation, an audit trail provides an equivalent to this information.

9. Annex 11 and other guidelines stipulate that the audit trail must be checked "regularly". However, is it really stipulated in some way that this must be done before the product is released?

Dr Wolfgang Schumacher

The regular check of the audit trail, which had been required since its publication in June 2011, was frequently questioned by representatives of the authorities at conferences and seminars. In all these discussions, the authorities rated the approval process for a pharmaceutical dosage form (final release for sale) as the most important process step of all, since no further reviews are carried out at a later time. Thus, the final steps determining quality are the inspection of the manufacturing protocol, the quality control protocol, the audit trail review and the implementation of the batch status from "quarantine" to "released" in the ERP system.

10. Audit trail review only for critical data: Does this mean that only systems with data that have a direct influence on the product can be audited? Not for systems with only an indirect influence?

Dr Wolfgang Schumacher

In deciding whether a review of the audit trail is required, several factors need to be considered: If it is not possible for the user to change/delete/supplement data after the initial entry, a review of the audit trail is not necessary. Furthermore, systems that only provide "subordinate" data for batch release (e.g. dimensions of a tablet) can be excluded from the audit trail review. The criteria for this must be recorded in a written data risk analysis.

3.3. Visual Inspections

ECA Visual Inspection Interest Group, Q&A Document 2.0

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Manual Inspection

MI1 According to Annex 1 of the EU-GMP-Guideline, operators doing the inspection for particles and other defects should make frequent breaks from inspection. Are there any regulations concerning rest times and time intervals?

An interpretation of this requirement is not trivial. Sometimes, the companies interpret it in a significantly different way. In practice, for example, the following variants can be found:

- 55 minutes inspecting, 5 minutes break over a period of 8 hours
- 20 minutes inspecting, 20 minutes other activities over a period of 8 hours
- 20 minutes inspecting, 5 minutes break over a period of 4 hours

It is a known fact that this activity normally can be carried out successfully for a maximum period of 15 to 20 minutes. Insofar the provision "55 minutes inspecting, 5 minutes break over a period of 8 hours" doesn't seem to be appropriate. Ideally, the activity of inspection will be limited to 15 to 20 minutes. Afterwards a break for the eyes should be taken without carrying out any other activities.

MI2 Which requirements should there be concerning the requalification of the personnel carrying out the optical inspection? Are there specific time intervals to be observed and should the requalification be announced?

The pharmaceutical companies have different approaches concerning the time intervals for requalification. The intervals reach from each month to every two years. Every two years certainly is too long. This period of time is especially problematic if the person carrying out the inspections doesn't pass the requalification any more. Which consequences does this have for the batches inspected by this operator? Insofar it seems to be appropriate to choose a time interval that is as short as possible and to control the personnel for example by means of an AQL testing. Are test sets used in the context of the requalification this should not be announced before the qualification run. For this reason, it is advisable to requalify not exactly every six/twelve months, for example, but to do this on a random basis i.e. to lay down irregular time intervals. If test kits are processed in the context of requalification you need to think carefully about the question whether the test kits should be inspected directly in the morning or at the end of the day in the case of an eight-hour shift. Naturally, it is advisable to choose the worst case situation and therefore, to let the inspection be carried out at the end of the shift.

MI3 How often have employees of the manual (or semi-automatic) inspection to be trained? What does "regularly" mean in this context?

With regard to visual inspection, the difference between initial qualification and requalification must basically be made. Strictly speaking, requalification is an examination of the status of a person's qualification. It is recommended to re-qualify employees at least every 12 months.

MI4 Should the set of samples for the qualification (training) of the staff be taken directly from the production rejects or should it be produced artificially based on typical defects?

Usually, the training set should be taken directly from the production rejects. Unfortunately, some failures occur only very rarely so that you have to produce some of them yourself. Finally, you have a set with failures that are typical for the production that has to undergo a formal release procedure described in an SOP. This guarantees that the failures are typical and that you can use them for training.

MI5 Are there empirical values about how long do lamps in semi-automatic testing stations keep their intensity?

Here, the certificates of the lamp manufacturers should be consulted. Usually, 2-3 years are indicated. In many companies, the lamps are exchanged routinely after one year to never have to question the test results due to possible lamp weakness retrospectively.

MI6 We have trained our inspection team to inspect containers in less than 5 seconds against a white and black background. Moreover we do an AQL testing afterwards and if the AQL fails the qualification status of the inspector will also be evaluated within a deviation. So is it allowed so shorten the inspection time?

Ph.Eur. and USP requirements for particulates are clear – manual visual inspection for 5 sec in front of black and white background is required. Annex 1* of the GMP guidance document states to use a given time and given set-up for inspection. Any modification must be validated and should show to be equal or better than the compendial approach.

*(Vs. 2008 rev.)

MI7 According to Ph.Eur the light intensity should be between 2000-3750 Lux but according to USP 790 it should be minimum 2000-3750 Lux. Is it ok then that the light intensity is higher than 3750 Lux?

The "minimum intensity" in USP <790> refers to 2000 Lux. But higher intensities as 3750 Lux or higher are possible and acceptable for certain types of products (e.g. Blow-Fill-Seal container). But operators fatigue will be higher and you have to adopt the eye breaks and the inspection time per day accordingly.

MI8 Is the wearing of anti reflective eyewear by manual inspectors a common practice among pharmaceutical companies during Manual or Semi automatic inspection as a measure against fatigue?

Wearing anti reflective eyewear is not the way for improving the quality of the visual inspection. On one hand a high light intensity can be necessary, on the other hand the tiring of the human eye seems to work contra productive to the detecting of the defects. One has to find a way between both effects meaning: use more eye breaks when using light with a higher intensity.

MI9 Is there a requirement in regards to the size of the visual inspection booth, e.g. width, length, etc?

No

MI10 How can foreign particulate matter be distinguished from a micro bubble in a vial that can form during vial stirring during manual inspection?

Up to now there are limited technologies for distinguishing air bubbles and real particles. Cameras and the human eye cannot see a difference when the particles/air bubbles are small. The only way is to avoid air bubbles. One approach is the use of two cameras. In case particle-camera1 detects something but particle-camera2 (under the same conditions as camera1) does not, it is likely an air bubble.

MI11 What exactly is meant by point 2.1 of the best practice paper ("The relative humidity and air velocity should be controlled and ensure comfortable working conditions.")? Is a permanent room monitoring required?

It is a fundamental GMP requirement: the fulfilment of a requirement has to be documented. A permanent monitoring of temperature and humidity may not be necessary, but how to prove during an inspection, that the working conditions for the human inspectors have been adequate? This will not be possible without measuring temperature and humidity and some sort of system, meaning the documentation and evaluation of measuring data. If this is not part of the building control system anyway, a manual system may also be possible.

Automated Inspection

AV1 The grey portion of fully automatic control is often checked manually, to return not clearly or fully tested products back to the inspection process. Is it allowed to carry out this testing with the automated inspection machine?

From a GMP view, there are no restrictions. It is also important here that at the end a yield calculation and evaluation in the batch record appears. And there are also automated inspection systems that have already integrated the double inspection with multiple cameras.

AV2 Can one reject test be considered as a good after two "good" inspection on the same machine?

This is possible in a few cases where - for example - the machine stopped and goods were therefore ejected. Otherwise, "reject" should always remain "reject". This is particularly applicable to "bad" goods which have been rejected because of particles or opacity. Containers sorted out due to cosmetic defects are however usually being re-inspected

AV3 We produce a lot of products with different formats. Until now we use a rejection rate of <2% as acceptance criterion and sets of samples from production to control the functionality of the machine.

An AQL test should be carried out for each batch. In the meantime this is expected by the authorities and inspectors. This is also described in the ECA Good Practice Guide on Visual Inspection. A control of the rejection rate of the 100% inspection is also expected but it rather serves for recognizing whether a batch differs from the normal unobtrusive production. This trending limits should be product specific. A generic limit eg <2% would need a rationale.

AV 4 In highly automated manufacturing lines for LVP flexible containers, the visual inspection process may/cannot comply to the standard visual inspection criteria e.g.: 5 sec inspection time, agitation of the container etc. Is this a compliance problem?

The requirements like 5 sec inspection time required by pharmacopoeias are addressing manually performed visual inspection. If the visual inspection is performed automatically, it is the company's responsibility to ensure that the inspection via camera systems is as effective as a manual visual inspection via a validation (e.g. Knapp Test).

AV 5 Do we have to perform challenge test before production / shift to check the 100% automatic visual inspection? And how often?

A function test kit (system suitability test kit) used before and after the inspection of each batch to demonstrate the functionality of the fully automated inspection system. It may contain an abridged set of more apparent defects such as big particles, cracked or empty containers.

Qualification /Validation

QV1 In the course of validation and during operation there are recurring problems with false reject rates in the case of fully automated systems. Are there any GMP requirements concerning this?

Due to the fact that the systems are able to detect also considerably smaller particles than human operators there are repeatedly emerging more or less big amounts of objects in the part with defects that have been assessed by a human operator as being good. Furthermore, a fully automated system might also get problems with air bubbles and reject these objects as having defects. In the end, the trick is to configure the system in such a way that no objects containing very small particles are rejected. In some companies the objects rejected by automated systems are again inspected by human operators. But this method entails the risk that objects actually having defects are suddenly classified as having no defects by the human operator. Two conclusions can be drawn from the point of view of GMP. Rejecting objects without defect does not entail a risk for patients and thus seems to be practicable. On the other hand one could also criticise the qualification as such since a system making errors is not sufficiently qualified. In any case, acceptance criteria should be defined for the part with defects. In the case of exceedance certain measures are to be taken such as an additional 100 % inspection for example. To sum it up: there is no requirement to set a limit for false rejects. But on the other hand it is advisable to also set a limit for the false rejects, usually during the qualification/5000 test. Because having no limit or a very high number of false rejects may question the whole qualification during a GMP inspection.

QV2 We have about 50 different aqueous solutions for a few hundred products (one solution for several formats). So far we have prepared one set of samples (function set, qualification set including Knapp set) from production rejects. This is very time-consuming. Do you think it might be useful to measure parameters such as viscosity, surface tension of the 50 solutions in order to group the products (bracketing)?

Bracketing is useful here. The rationale using viscosity is ok.

QV3 Which statistical tests should be applied to demonstrate equivalence of different visual inspection processes (e.g. manual versus automatic inspection process)?

The goal of the AIM qualification is to show that the machine is equal or better than the "gold standard" that is the human inspection. This can be done by comparing the overall detection rates for particles (this set also includes non-particle objects) and at least 10 inspections runs of this set for manual inspection (normally 3 operators) and the same set of objects on the machine. For non-particle defects (scratches, missing stopper,...) one could use a predefined limit or also a man/machine comparison.

Test Sets

TS1 What are the differences between qualification, particle (Knapp test) and function test set?

The function test set serves for a sort of system suitability test, i.e. this test is used to test before and after each batch whether the cameras are functioning correctly. Usually, no challenging samples are used for this, but rather unities with particles having a detection rate of 100% such as particles with a size of 1000 µm, vials with missing stoppers.

Qualification test set: the qualification test set consists of product specific containers containing the product and having all known "static" defects (scratches, wrong flip-off, missing stopper,...). Usually, about 10-20% of the containers of the set have a defect. New failures or defects are added to the qualification test set.

Particle test set (Knapp-Test): Sets that contain only particles. These are particles having the size from 50µm to 1000µm and consisting of different materials (plastic, the material stoppers are made of, glass, metal). Hence, they are "non-static", i.e. the defect is in the container or in the drug solution. Particle test sets are part of the qualification test set at the same time.

TS2 Should all these test sets be prepared artificially? Should this be done, for instance, by an external laboratory with defined failures?

We prepare the static defects in-house and a part of the non-static defects (particle defects) are produced externally. But it is also possible to have everything produced externally. But the static defects should be the same that are generated in the worst case by your production machines. Therefore, I advise to make these in-house and get the release from QA. In this way you would have representative bad samples from your process. In the best case you take bad samples from your process but it is not possible to do this for all samples

TS3 The problem is that sets of samples have to be remade regularly since they have expired. How do you prepare the function test set?

Usually, our sets keep several years. Single samples have to be replaced again and again. These single samples are then released by QA and we introduce them into the set. The sets should be controlled at least once a year and be released again afterwards.

TS4 How long can a training kit be used?

Training kits should contain all kind of defects and must be updated constantly with new evolving defects out of production. Expiry of specific defects depends on nature (a crack will not expire; small particles may clot together...). The set must be regularly released and reinspected by a supervisor.

TS5 How should qualification sets be prepared for a new product?

All representative defects coming from a production line should be included in the set. Some of the defects need to be generated but if possible should be taken from production. These defects need to be classified. See chapter 5 of the Best Practice Guide.

Requalification

RQ1 If systems for the fully automatic visual inspection are used, regular functional testing is carried out. Must the system be requalified nevertheless?

According to EU-GMP a difference must be made between the following activities in the case of a fully automated system:

- Qualification: in the case of new equipment
- Requalification: Assessment of equipment within defined time intervals
- Functional testing: Test carried out before start of work (and preferably also after work)

- Periodic evaluation: According to EU-GMP Annex 11.

Functional testing addresses the sensor functionality only and is typically carried out before and after batch inspection. Due to its limited scope, functional testing cannot replace requalification of an equipment. Requalification should be performed according to the EU-GMP Annex 15 to safeguard that the whole equipment remains in a state of control. Requalification programs and intervals shall be planned and justified according to the guideline. In the context of the assessment of the facility, the functional testing carried out until the date of requalification will certainly be part of the assessment.

RQ2 Requalification: If the regular requalification of the automatic inspection machine is carried out by means of the test of 5,000 does this mean that the 5,000 vials from one production batch must all be controlled manually and by the automatic inspection machine?

I.e. is it necessary to repeat the man-machine-comparison that was carried out in PQ? Almost correct. PQ consists of the particle (Knapp test) run, the run concerning the "static" defects and also of a run of 5,000 of GOOD vials. This run of 5,000 is carried out once a year for each product. The Knapp test and the "static" test are not repeated except when there have been changes at the particle detection stations. Without changes (something that occurs only very seldom) only the test of 5,000 is carried out, i.e. 5,000 vials from the automatic inspection machine are inspected by a person and by the machine

AQL-Testing

AQ1 Is AQL testing mandatory as a part of the visual inspection?

A direct requirement cannot be derived from the EU GMP. Yet, the AQL tests correspond to the state of the art in science and technology. Since we know that neither a manual nor an automated visual inspection can guarantee a 100% particle-free batch, an additional measure - like the AQL tests - is certainly appropriate. Another method would be of course a second 100% inspection. Or you could show in the validation that the test method used is a 100% flawless and complete, what will hardly be possible in practice. For US, the AQL testing has been included in the USP, chapter <790>.

AQ2 Do the European agencies follow the rules for AQL testing given in USP <790>?

There is no written guidance in Europe requiring an AQL test according USP <790>. Companies have to define their own way to implement a check of the visual inspection efficacy.

AQ3 Should the AQL be inspected by QC or production

AQL manual inspection may be carried out by production staff (to avoid setting up a separate visual inspection team in QC) under a quality oversight or the quality unit. If performed by production operators, the AQL test should not be done by members of the team that was performing the 100 % visual inspection of the batch.

AQ4 Is the AQL acceptance criteria of 0.65 for the particles only or for the overall defects?

USP <790> addresses visual inspection for particles. So the requirement to apply an AQL of 0.65 or sample plans with better protection applies to particles. Other defects like cracks or stopper failures may be addressed with tighter AQLs.

AQ5 Which sample size should be taken if various AQL-levels depending on the defect criticality are used (for example batch size of 22.000, AQL = 0 for critical defects, AQL = 0.65 for major defects, AQL = 2.0 for minor defects)

There is a misunderstanding. The sample size is depending on the Quality Level one wants to use (e.g. level II). With this level and the batch size one gets the size of the sample which must be drawn. The AQL level (e.g. 0.65) then defines how many defects are allowed to accept the defined batch quality. Of course the AQL level then depends on the criticality because the more critical the less defects are allowed to be found in the AQL procedure.

AQ6 For vials packaged in separated sub-batches, when the 100% visual inspection is located at the beginning of the packaging process, should the acceptance sampling be statistically significant on the full manufacturing batch or on each single sub-batch?

The AQL sampling should be based on the sub-batch meaning the batch size that is inspected. One is checking with this test if the incoming quality of the batch is according the quality which is expected. The levels do not need to be the same like for the initial batch.

Defect Categorisation

DC1 The USP in sections 790 and 1790 classifies glass defects as a major defect. There are many types of glass defects, e.g. glass particulates adhered to the side of the vial, and loose glass within a vial (in both incidents if product integrity/sterility assurance is not compromised), could you please tell me what the defect classification levels (critical, major or minor), for either of the former mentioned defects should be.

Both USP chapters do not make any classification of defects. This needs to be done by the pharmaceutical company and has to be based on a quality risk assessment

DC2 How should freeze-drying defects such as collapse and melt-back be classified regarding to their criticality

In the scientific literature a melt-back is seen to be critical. The difference of a collapsed and a melt back is difficult to define. A collapsed lyo cake could also be a melt back. One would need to explain this difference and its criticality.

Special Products

SP1 Our DP is a powder. Is visual inspection of the reconstituted solution sufficient?

100% visual inspection of the delivered DP is a general requirement. The inspection of the reconstituted solution would be part of the release process. According USP<1790> special sampling plans according S-3 and S-4 (ANSI/AQS Z1.4) should be used.

SP2 How should the operators performing the supplemental testing be qualified?

Supplemented testing is performed on reconstituted vials and thus has to be performed in a lab environment. The reconstituted vials are tested either by manufacturing operators or QC staff based on the same criteria as training for 100 % visual inspection or AQL testing.

SP3 What is the recommendation for AQL setting for the testing of samples after reconstitution?

This depends on the nature of the product. Taking 0.65 will in many cases disqualify nearly all batches. In some cases it might be an option to allow a second level testing to avoid that 1 single particle in one vial out of 20 requires rejection of your batch.

Regulatory Affairs

RA1 If the 100% visual inspection is followed by an AQL testing, do we have to perform also an test on visual particles at the release (testing) of the batch?

The AQL testing is intended to replace testing for visible particles at release testing in the lab. However, if this test is part of your filing, this has to be done. Or you have to file a variation.

RA2 Is the carrying out of a 100% inspection of parenterals to be understood as IPC testing or as final product testing? Is it possible to carry it out under the responsibility of production or must it be done by QC?

Assigning the activity of a 100% inspection is not trivial at first sight. Formally, this activity is allocated to production. By the way, this is also FDA's point of view. Hence, it also is an activity which requires a manufacturing authorisation within the meaning of § 13 German Medicine Act (AMG). Due to the fact that it is a 100% inspection, it is neither a real IPC nor a final inspection on a random basis. The 100% inspection being attributed to production, it is carried out under the responsibility of the head of production

RA3 Are there legal acceptance criteria or provisions regarding the size of (visible) particles?

According to studies by Jules Knapp, people can recognise particles under optimal conditions from 30 - 50 µm, taking into account the colour of the particle. Other studies have shown that eventually

particles from approximately 200 µm can be surely detected - in other sources, values of 50-80 µm can be found. There are (still) no statutory limits on the size of the visible particles

RA4 What does essentially free from particles mean with respect to the US and EU pharmacopeia? Is there a difference?

Up to now there is no official statement from the EMA about the interpretation of "essentially free from particles".

RA5 How has the limit for inherent particles to be set in a registration of a new protein product which is known to form particles?

The guidance according USP<1790> would be to define a limit and to monitor this limit. Of Course this limit needs then to be described within the dossier of the DP.

Process Control / SPC

PC1 How can Process Control Limits in the Visual inspection process be defined?

Typical limits for product and production line need to be established. Therefore see chapter 6 of the Best-Practice Paper. This follows the ASTM E2587-2 standard (Standard Practice for Use of Control Charts in Statistical Process Control).

3.4. Qualified Person

Q&As at the QP Forum 2016 in Madrid, Spain

Q: If you want to qualify a wholesaler that will provide me with commercial products for the use in clinical trials, as a comparator or for the manufacture of IMPs, what controls are expected to ensure that the wholesaler doesn't provide me with falsified products? What if the wholesaler is not willing to disclose the supply chain?

A: a) The wholesaler should be qualified by an audit (e.g. check facilities, availability of licenses, e.g. MIA for importation of third country comparators, supply chains for comparator sourcing, tools; please do also refer to the presentation of Mr. Paul Hargreaves, MHRA at QP Forum 2016).

A quality assurance agreement should be in place to agree on the sourcing supply chains, regular check for recalls by the wholesaler, rapid communication line, etc.

b) In this case it is recommended not to use the wholesaler.

General remark: Within the TransCelerate initiative a comparator network has been established. More information is available on the TransCelerate website.

Q: If more than one third party manufacturer is listed [in the dossier], do we need to keep them all "active" to start production immediately if needed?

A: For EU Health Authorities the expectations are clear on having all registered parties qualified and prepared for their intended manufacturing activity/ies as well as having all active parties within a supply chain being registered.

Q: What is the QP responsibility when it comes to audits performed by the API manufacturer of their suppliers? Should our auditor look at the audit programme of the API manufacturer? Can we demand to see the respective audit reports?

A: Directive 2001/83/EC in correspondingly chapter 5 and Annex 16 all define the supply chain starting from starting materials for API manufacturing down to the point of certification. Correspondingly all involved parties should be subject of GMP and audits and subject to QP GMP compliance assessment. Audit planning and audits execution as well as the handling of observations and deviations from GMP on any party within this supply chain including any suppliers should be a routine subject during audits.

Q: If we have audited our API supplier more than three years ago, would a remote (paper based) audit be sufficient?

A: Within your Quality system strong risk assessments procedures should support your approaches. Dependent on your risk assessment a longer period may be acceptable to support the needs of the QPs assurance of GMP at your API supplier. Any issuance of a QP declaration should be supported by such risk assessments, if no audit report younger than 3 years is available. – It is upon the discretion of the QP, whether he is satisfied to assess and confirm GMP compliance on such basis.

Q: An MAH has a technical agreement in place with a CMO for the manufacture of medicinal products. MAH has audited CMO and has delegated the responsibility to audit the API supplier to the CMO. The CMO does also manufacture APIs for some of our products. Is it acceptable for the QP of the MAH to create/ sign the QP Declaration on the basis of audits performed by the CMO, which in some cases are self inspection reports?

A: An API manufacturer usually does not have a QP and such API manufacturing activities should not be part of the same manufacturing license of a drug product manufacturer where the QP is situated, even if both activities are executed at the same company/site. From the perspective of the QP it should be ensured, that QP declaration should refer to audits performed by personnel not belonging to the API manufacturing organization. As such personnel from the drug product manufacturing organization or an independent party (refer to Annex 16) should have performed such audits. Additional explanation may be given in the respective field of the template.

Q: Is there a time period defined for prospective validation? How much time would be allowed to complete a prospective validation?

A: No definition in EU-GMP requirements about any time-frame.

Q: Can we transfer a product from one warehouse to another warehouse before the product is certified for release?

A: Annex 16 chap. 4.1: Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant Competent Authority.

Q: Data Integrity: what do you expect to see in a company? SOP/ Policy on Data Integrity, computerised systems, processes? Anything else?

A: If requirements from Annex 11 (computerized systems) for electronic data and EU-GMP Guideline Part 1 chap. 1 (documentation) for paper based documents are fulfilled in conjunction with "good documentation practice" there need no additional documents to be created to assure or proof data integrity to EU-authorities.

Q: Scale-up batches: can I certify them for release and sale?

A: Annex 15 chap. 5.8, which is on validation for commercial products/processes: Normally batches manufactured for process validation should be the same size as the intended commercial scale batches and the use of any other batch sizes should be justified or specified in other sections of EudraLex, Volume 4.

Only for submission batches other batch sizes may be possible acc. EMA-Guideline on process validation for regulatory submission (separate guidelines for medicinal products and biotech-products). Batches can only be commercialized, if they fulfil all Annex 15 requirements.

Q: Concurrent validation: the first batch passes, the second batch fails. Do I need to recall batch No. one?

A: That is to be discussed with the competent authority, because there is no detailed requirement exactly for this case. Annex 16 chap. 1.7.12 says, that batches can only be certified if process is in a validated state. Therefore the requirements for certification are retrospective not fulfilled for the first batch. Definitely your validation master plan or validation plan should predefine how to deal with the situation of failure in concurrent validation.

Generally, concurrent validation pre-sets a detailed product- and process-knowledge, which from my point of view is not existing, if this happens. That's why, concurrent validation is the wrong validation-approach for such a product.

Your approach on such a situation should be synchronized with your competent authority to be on the safe site.

Q: After a successful accelerated stability study, the long term stability study fails. What is expected to do with the batches manufactured between accelerated study and long term results?

A: Annex 16 chap. 1.7.14: Any regulatory post-marketing commitments relating to manufacture or testing of the product have been addressed. On-going stability data continues to support certification. Following from this, certification requirements are not fulfilled. Batches can only stay on market as long as on-going stability data show stability over shelf-life.

Q: Serialisation of multi country packs: Reimbursement codes are included in the matrix, making the matrix code unique for a country. How can we deal with multi country packs?

A: As I understand the system, a unique reimbursement code will be included in the matrix, once a pack is assigned to a country, this code will be cross referenced to the country's reimbursement system. If a pack is reassigned to another country, then the reimbursement code will be cross referenced to the new location. Please note that the matrix can be cross referenced to any country it is destined to, there will be no physical reimbursement label on the unit, therefore it is possible to reference the number. This is very different to the current ways of working the new process has been designed to cater for such events.

Q: Correct wording: what is the difference between "Certification" and "transfer to saleable stock"? Can an MAH perform batch release only based on batch certification performed by an external QP?

A: The process of batch release includes the following steps

The checking of the manufacture and testing of the batch in accordance with defined release procedures.

The certification of the finished product batch performed by a Qualified Person, signifying that the batch is in compliance with EU GMP and the requirements of its marketing authorisation (MA)

This step is called "Quality Release"

Once the QP has signed the register, the batch can be transferred in a third step to the saleable stock – either by assigning a release status in an ERP system or by affixing "release labels".

This is the final step in the process which effectively releases the batch for sale or export. This could be done by the QP as an integral part of certification or it could be done afterwards by another person. If this is delegated to another person, this has to be covered by a SOP or contract.

Q: Annex 16, 2.2 requires: "audit report should address general GMP requirements, ..., all relevant production and quality control procedures related to the supplied product...". To what extent should this be done? Is an audit of a contracted manufacturer expected to last 2, 3, ...10 days? Are one or more auditors required?

A. The points to be covered in an audit may be derived by the EMA Q&A that is dealing with the particulars that have to be reported in an audit report of an API manufacturing site. The same or even more is requested to be documented in case of the audit of a contract manufacturer for finished products.

Usually two auditors are better than one and the audit should last at least 2 full days for an initial audit.

Later for re-qualification audits this may be reduced to one day.

Q: Where do you see the QA department/ Quality Unit? I have the impression that the QP needs to be involved in everything. Does QA/QU have no responsibility?

A: Discussing the manifold activities the QP is involved in should not indicate the QP is responsible for everything. EU GMP part I, chapters 1, 2, 5, 6, and 8 are describing numerous responsibilities of other key personnel at a pharmaceutical manufacturer – e.g. Head of Production, Head of Quality Control, Qualified Person for Pharmacovigilance. The revised Annex describes in detail in part 1.7. what activities may be delegated to these key personnel and how the QP can rely on these activities and the Pharmaceutical Quality System. According to the EU GMP Guideline, Part I, Quality Assurance is a system rather than a department.

Q: Elemental Impurities: Will it be necessary to submit variations to the national competent authority, following the risk assessment? What about those cases where results are above and below the threshold?

A: No variation has to be filed if the risk assessment and the supporting tests clearly indicate that no further controls, or replacement or change of quality of starting or packaging materials used, or change of the manufacturing process are needed. If any of these points is needed a variation has to be filed

Questions and Answers QP Forum 2015, Berlin

Q: Is the written confirmation for the import of APIs also applicable for IMPs?

A: No. Active substances used for investigational medicinal products or for medicinal products intended for research and development trials are excluded from the rules. (Source: "Importation of active substances for medicinal products for human use, Questions and Answers / European Commission, Vers. 4.1, Question 3").

One known exception is Germany: Active substances used for IMPs are not exempted from §72a Arzneimittelgesetz (German Drug Law).

Q: Difference IMPs - personalised medicine: which licence will cover personalised medicine? IMP or Specials? How can the labelling be handled according Annex 13?

A: European Legislation currently permits access to personalized medicine via two routes,

- Dir 2001/83/EC Article 3 (7) - the hospital exemption scheme for ATMPs, or
- the "specials" scheme (Dir 2001/83/EC Article 5).

Source and further information: JD Johnston, P Feldschreiber, Br J Clin Pharmacol. 2014 Jun; 77(6): 939-946.

It is recommended to clarify with the responsible inspectorate which licence will cover the personalised medicine in the specific case.

Further specifics for labelling may be found in the EC's consultation document "GMP for ATMPs" (July 2015). An example for labelling is included in the presentation "GMP for ATMPs", K. Hoogendoorn (IMP Pre-conference 2013) and can be provided on request by the IMP Working Group.

Q: As a wholesaler we receive from time to time from the manufacturer a CoC which is not approved by a QP. A "QA authorized person" has in some way released the product for sale. Is this allowed? The manufacturer explained that in some in EU countries it is not required that the QP approves the CoC. What could we do as a wholesaler?

A: Another appropriately trained person other than the QP can release the product (transfer the product to saleable stock). This does not include the possibility to delegate the signature under the certificate. According to Annex 16 Annex II certification statements require signature of the Qualified Person.

Q: According Annex 16, 8.3, a QP should maintain knowledge and experience up to date in the light of technical and scientific process and changes in Quality Management. How can this be demonstrated?

A: Each QP should have the concept how he maintains his knowledge and experience documented based on an assessment of need dependent of the responsibilities taken. Training documentation should be available in appropriate depth to document, that the concept is followed.

Q: New Annex 16: in the case of deviations, the root cause should be corrected prior to QP certification and/or sufficient level to support certification should be provided. What is the difference? How should this be handled?

A: Chapter 3 of Annex 16 discusses the handling of unexpected deviations in relation to confirmation and certification by the QP. The deviation management system should ensure that deviations are thoroughly investigated and the root cause corrected. In combination with 1.7.16 All investigations pertaining to the batch being certified (including out of specification and out of trend investigations) have been completed to a sufficient level to support certification.

the confirmation or certification may be performed prior to formal close out of the deviation or complete effective correction of the root cause. This is restricted to such cases, where deviations are unexpected excluding repetitive confirmation and certification for later batches with continued open deviations or not corrected root causes.

Q: New Annex 16: Sampling in a third country now requires comparative analysis, random periodic retesting etc. Furthermore, any unexpected or confirmed OOS result has to be notified to the competent authority as a potential quality defect even if the batch was not certified and released to market. Why should the competent authority be notified if the batch will not be released?

A: Scrutiny is given on the sampling in a third country. Precondition have to be met and surveillance of the establish processes have to be ensured. These provisions intend to ensure that the importer does not receive a perfect sample but falsified product. Any signals like any unexpected result or confirmed out of specification result during the importation testing do not only indicate that the batch concerned may be falsified but also that the measures and controls in place to avoid falsification may not be sufficient. The approach is comparable with handling of unexpected results in the stability programme.

Q: From my experience, FDA is "not amused" if inspectors from the EU competent authority are present during an FDA inspection. What is your experience?

A: Normally we [EU Inspectors] are informed from our companies about the FDA inspection. Amused or not, if we want to participate we will participate. But I did not have the impression that they do not like it if we accompany them.

Q: Ambient transport (15 - 25°C): do you think that it is justified to predefine tolerance for temperature excursions (for example 24h between 25 and 30°C or 6h between 30 and 35°C) without handling an occurrence as a deviation? Might the Mean Kinetic Temperature evaluation help?

A: This might be an option if competent authority agrees, but ONLY if all temperature excursions from end of production are summarized. As a consequence you need all excursions from the whole supply chain. Whether it is a deviation or not depends on the criticality and your QA-System. In any case it must be assessed.

Q: Annex 16, 1.7 (additional pre-requisites to be fulfilled prior to batch certification): how should a QP behave if a Q-System of a company is not capable to provide all the requested data like for example assurance of appropriate GMP requirements for excipients (risk assessment missing). Should I refuse final batch certification? Should I inform senior management and certify the batch? Or anything else?

A: : From 21 March 2016 Excipient Guideline is in operation. From then requirements need to be fulfilled. Guideline was published one year in advance, though there was/is enough time for at least defining excipient-risk-profile and defining appropriate GMP by medicinal product manufacturer. This must be taken into consideration for batch certification. Enforcement of defined appropriate GMP requirements at excipient manufacturers might take some more time.

Q: According Annex 16, 8.3, a QP should maintain knowledge and experience up to date in the light of technical and scientific process and changes in Quality Management. What do authorities expect?

A: E.g. detailed product and process knowledge. Knowledge on new implemented regulatory guidelines. Participation in change control system.

Q: As a virtual company, do we need access to the "Medicines Verification System"? Can we delegate this to our CMO (contract manufacturing organization)? Do I need to verify serialisation at release stage?

A: As a virtual company you do not have to perform this. The verification of serialisation should normally be included at the release stage from the manufacturer, which also includes CMO.

QP Association - Publications

European Qualified Person Association - Publications/Question and Answer Documents

How to become a Qualified Person

Q: I am a Chemist. How can I become a QP?

A: In Article 49 of Directive 2001/83 (for veterinary medicinal products, please read Article 53 of Directive 2001/82) – please see the QP Regulations, the qualification level as well as the necessary professional experience of a QP is defined. The EU requirements as defined in these Directives have to be transferred to national law in each EU Member State. However, there are a number of differences in the EU Member States due to the fact that each Member State can implement the directives into national law with slight modifications.

Our recommendation is to discuss this matter with the respective authority in the Member State you plan to work as QP.

Q: Can companies outside the EU but with an MRA have a QP according the EU Directive. Can such a person be certified by the EU?

A: Things that need to be considered are:

1. The QP is linked to a European Manufacturing authorisation.
2. If the "QP" is an employee of a company outside the EU, he/she is not employed by a company with an European manufacturing authorisation and therefore can not act as a QP.
3. There is no such thing as a certification to be a QP. A QP is registered by the authority of the respective EU member state.

It is normal practice for a product manufacturer in a third country to have an EU-based importer who can provide the services of a QP? This EU-based QP would assess and certify a product/batch imported into the EU.

Q: Does a QP from an EU Member State who is appointed by the Member State's Main Pharmaceutical Inspectorate as a QP and is chemist and not a pharmacist can move to Germany and still carry out duties of QP?

A: Although the educational background would not be considered sufficient by the various local authorities in Germany to be initially accepted as a QP, a Chemist would be accepted once he/she is

registered as a QP in another Member State. So once a QP is eligible and registered by another Member State authority he/she could apply as a QP in Germany. However it needs to be decided by the local German authority (e.g. Regierungspräsidium or local government). Many Member States require that a QP speaks the local language to be able to understand batch records, certificates and other GMP-related documents.

Q: If a company is based in Switzerland and produces pharmaceutical products, what are the possibilities to become a QP

A: As Switzerland is not an EU Member State, the applicable Directives apply via the MRA. The QP in Switzerland is called the "Fachtechnisch verantwortliche Person". To become a Fachtechnisch verantwortliche Person, an academic qualification is needed (for finished products and intermediates usually a pharmacist). Other academic qualification is acceptable in case of proven experience and for APIs and blood products. The Notification is handled by Swiss Medic and the "Fachtechnisch verantwortliche Person" will be named on the manufacturing license. We would recommend contacting Swiss Medic for further information.

Q: There are certain professional bodies in UK who can grant QP status and can advise people that they are eligible for QP status as per EU Directives. However, it appears that some Member States do not recognise the defined education and experience requirements for becoming a QP as per EU Directives. In France for example the 'Pharmacien Responsable' has to be a pharmacist qualified and registered in France. Is it possible to operate as a QP recognised by markets where our products are commercialised (all EU), while not being considered a QP by the country of manufacture?

A: Directives are only binding as to the result to be achieved– and leave national authorities the choice of form and methods. The EU requirements as defined in the Directives have to be transferred to national law in each EU Member State. However, there are a number of differences in the EU Member States due to the fact that each Member State can implement the directives into national law with slight modifications. This national law is the binding one. To operate as a QP one has to be named by the holder of the marketing authorisation in the EU and must be registered/ accepted by the EU member state where the company resides.

Duties and responsibilities of the Qualified Person

Q: A company has recently been inspected by the respective national Inspectorate, and some of the observations in this inspection related to the role of the QP with respect to the quality system. For example, the authority asked for a description of the QP's responsibility with respect to the approval of controlled documents (documents in the quality system). Is this required in the QP relevant legislation?

A: It is a common misconception in these days that the QP is considered being responsible for all aspects of a Quality Management System, especially for approval of all kinds of documents, forms and reports.

Although the QP's tasks and responsibilities are manifold it must be clearly stated that a QP is not automatically the Head of a Quality Management System, Head of Quality Assurance, or Head of a Quality Control Unit. This may be the case in smaller companies but very often, this is not the case. The QP then has to rely not only on other QPs but also on other staff and the Quality System, especially the Head of Production and the Head of Quality Control.

So it is the QP's duty to ensure that certain pre-requisites are fulfilled as described in Annex 16 to the EU GMP Guide.

There is no requirement in the European regulations and Guidelines that the QP has to approve any other documents than the release documentation. However, a QP should be involved in the implementation and maintenance of the Quality (Management) System. But the QP is not obliged to implement and run the Quality System.

So if a company has a Quality Control Unit and/or a Quality Assurance Unit with experienced and authorised staff - why should the QP approve controlled documents?

Contract Qualified Persons

Q: Is there any guidance available defining "sufficient" time on a site to familiarise a Contract QP with the Quality System?

A: There is no guidance available. The time on site will depend on the complexity of the quality system. An important consideration is the maturity and stability of the system. If the system is mature and stable a shorter time on site may be indicated, provided that the contract specifies that the QP must be made aware of any changes that affect the quality system.

Q: Outsourcing the QP batch release:
- what are the pre-requisites (GMP and legal)?
- what experience is needed?
- are there any existing models as a reference?

A: The QP must be endorsed by the competent local authority according to the national law. There must be a written agreement between the QP and the manufacturer, clearly describing the role and responsibility. The permanent availability of the QP must be assured, the frequency of on-site availability and the way the QP gets all relevant information must be defined. The QP must be appropriately experienced in the manufacture and quality control of the product type manufactured by the contract giver. In case the products need additional formal education or experience – like with regard to blood products, the QP must comply with these requirements.

Q: When IMPs are imported from outside the EU; how could I set up a working relationship as a contract QP when it comes to liability and insurance?

A: As a contract QP you are a "normal" contracting party (i.e. just like any other service provider for the company but with the specific legal responsibilities and risks of a QP) and therefore no employee of the company. That means that you are not covered by any of the insurance programmes which companies usually provide for their employees (e.g. D&O insurance). As a result, you should mention that fact – and the related legal risks – during your contract negotiations with the company.

Ideally, there should be an indemnification clause in the service contract providing for that 'the company indemnifies the contract QP from any and all third party claims related to the services which the contract QP may perform under the service contract'. If your current contract does not contain such provision, you should ask the company to sign an amendment with aforesaid clause.

You can also ask the company to get yourself explicitly included in its D&O insurance contract (some insurers may actually be ready to do so because of the specific situation of the contract QP). This inclusion could be the first part of the contractual provision, followed by the indemnification clause mentioned above.

Release Decisions

Q: An API is contaminated with very small amounts of glass (<0.02%). The API is micronized and then pressed to tablets (oral). Giving the fact that glass has a very low toxicology; would you release the batch of the final product?

A: No. There is an excellent quote in the European Pharmacopoeia, Chapter 1. "General Notices, Tests and Assays": "... It is not presumed, for example, that an impurity that is not detectable by means of the prescribed tests is tolerated if common sense and good pharmaceutical practice require that it be absent." Good Manufacturing Practice and Good Pharmaceutical Practice require glass particles to be

absent in APIs that will be used to manufacture oral solid preparations without any filtration step that would remove the particles! If during its production the API has undergone a last purification step by re-crystallisation after filtration using charcoal or a filter aid, this step should be repeated with the contaminated API (reprocessing) to remove the contaminant.

Q: A sterility test failed most likely because of a contamination during testing: is a re-test justified?

A: A retest of a positive sterility test must be very carefully justified based on a root cause investigation giving evidence that there has been a contamination in the laboratory during preparation or testing. It is not appropriate and acceptable to re-test based on mere suspicion. Reasons to invalidate a positive result would be e.g.

- Microbiological monitoring of the sterility testing facility shows evidence for a failure like detection of the contaminant(s) in the testing environment. This has to be proven by genetic identity of both isolates!
- Microbial growth is found in the negative controls
- After identifying the microorganisms isolated from the test, the growth of this species can be clearly linked to failures with respect to the material and/or the technique used when conducting the sterility test procedure - e.g. contaminated media or non sterile sterility testing units

Q: A product (sterile eye drops) meets all specifications. However during production some microbiological monitoring results were not OK. Can I certify the batch?

A: Microbiological monitoring data are not describing the microbiological status of the batch itself. Monitoring data are considered to give information about the controlled environment. A level excursion in micro monitoring may be an indicator that there are deviations from the usual process, but they do not automatically indicate a microbiological problem of the batch. Following a positive outcome of a risk assessment of the non conforming monitoring results (type of contamination, level of contamination, place of the monitoring, other monitoring data, trending) it might well be possible to certify the batch.

Q: What should happen if OOS investigations are inconclusive?

A: The certifying Qualified Person should fully consider all of the information prior to making any decisions as to the final disposition of the batch. Any decision to release a batch where OOS results have not been invalidated should come only after a full investigation has shown that the OOS result does not reflect the quality of the batch. In making such a decision quality assurance and the Qualified Person should always err on the side of caution. (source: MHRA Q&A)

Role of the Qualified Person in the Company

Q: Is it possible to name more than one QP for the release of one certain product and if yes, can each QP be named as responsible for different sub-types of the product?

A: It is perfectly possible to name more than one QP and they can be named for different sub-types of product.

Q: Does the QP have to confirm acceptance of the company's QA-System in writing or is signing of job descriptions and/or signing key-SOPs sufficient?

A: There is absolutely no regulatory or GMP requirement or expectation that a QP has to sign off job descriptions or key SOPs. In addition there is no formal requirement that a QP has to "confirm acceptance" of the company's QA-System. Pharmaceutical manufacturers usually run regular Quality Management Reviews that include a documented management assessment of the suitability of the

Quality System. Therefore we would consider it appropriate and adequate that the QP is a regular member of this board.

Q: From a GMP and legal point of view, is there any problem that QP/QA and QC are the same person?

A: The only requirement under GMP is that the person responsible for production and the person responsible for quality control are independent. The QP can be the person who is also responsible for QC or the person who is responsible for QA (or both). In practice the QP certifying batches of product should not be the person who is responsible for their production.

Q: Who should sign the Quality Agreement? The QP only? QA? Legal? Head of production/QC? Business?

A: Quality Agreements should be considered GMP documents. Therefore involvement of the Legal Departments can be limited. According to the latest revision of chapter 7 of the EU GMP Guide ("Outsourced activities") ... 7.12 "A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice."

Chapter 2.7 of the revised chapter 2 of the EU GMP Guide ("Personnel") states: "The heads of Production and Quality Control generally have some shared, or jointly exercised, responsibilities...— the approval and monitoring of contract manufacturers;"

Keeping these two chapters in mind, I would advocate for the Head of Production and Quality Control to sign a Quality Agreement. The QP must be informed, but there is no obligation for him/her to sign the Quality Agreement.

Q: If an audit required by Annex 16 is performed by corporate QA or a global QA function of the same company but part of different legal entity (e.g. from US), will I need a contract or is an SOP sufficient?

A: European understanding on different legal entities even within the same global company has to be considered as independent to each other in terms of GMP. According to Chapter 7 EU GMP all services contracted out should be covered by a contract. If such a service is provided to the QP by a global function it should be covered by a contract. Topics to be considered are provisions of influence on sequence, audit agenda, audit reports availability, auditor rating and possibilities to accompany the audit as an auditor.

Q: Annex 11 states that "There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties." What should be understood by "close cooperation between all relevant personnel ..."? What formal requirements should be observed?

A: No defined formal requirements exist for close co-operation between all relevant personnel during validation. But efforts must be made to ensure that a corresponding division of roles and tasks between the relevant personnel is clearly defined and implemented, including IT. (source: ECA Q&A) QP Association - Publications

Role of the Qualified Person in the Supply Chain

Q: What are the most critical elements of the supply chain requiring QP involvement?

A: First of all QPs must define the relevant supply chain, for many companies this starts from procurement of the raw materials (e.g. APIs, excipients, packaging components etc.), ending when the product reaches the customer. The QP then needs to identify what input is required at each stage, then either personally provide that input or delegate the activity to another person or department within the company and ensure to stay informed.

Q: Where does the responsibility of the QP end? When the product is handed over to wholesaler/RP?

A: Normally once the product is delivered to the customer it is assumed that the customer will take responsibility for the product from the point of receipt. If the product is supplied to a wholesaler, it very much depends on who owns the product, if the wholesaler has purchased the goods, then they should take responsibility. However, if the product at the wholesalers belongs to the QP's company, then the QP continues to have the responsibility for the goods whilst at the wholesaler. The responsibility for the product at each stage of its life cycle should be clearly defined in the internal procedures, and where external parties involved (e.g. wholesalers) in the Technical (Quality) Agreement between the company and the wholesaler. It is possible for the QP to delegate this responsibility to the RP at the wholesaler, but this must be clearly defined (including the limitation which may apply) in the technical agreement. Please note that the QP retains the responsibility for recall of the products in the market place as well as ensuring that any product complaints have been fully investigated and appropriate corrective actions have been taken.

Q: What exactly is a GDP certificate? Will this be introduced in all Member States?

A: We are not sure if this is something every member state is going to issue after inspection. ?

The Qualified Person and Contract Manufacturing

Q: In case of an existing quality agreement, is it sufficient to rely on the certification of other QPs or should there be a review of for example batch records and deviations for the final batch certification?

A: In theory it is sufficient to rely on the certification of other QPs if the final certifying QP has knowledge of the other QPs and of the quality systems within which each of them is operating. In practice the final QP should be aware of any matter that might affect his/her decision to certify the batch (for example deviations or OOS results/investigations) and hence should review documentation from time-to-time, particularly if contract manufacturers and contract QPs are involved in the process.

Q: Is it allowed that a Quality Assurance function of the contract manufacturer can perform the audit of the contract manufacturer on behalf of the QP of the contract giver?

A: The audit must be performed by a qualified auditor who has no conflict of interest in the company being audited. This would mean that the contract manufacturer could not audit himself. But it would be quite acceptable to have an independent third-party auditor carry out the audit on behalf of the QP. It does not have to be carried out by the QP in person.

Q: PQR: A contract manufacturer is responsible for final batch certification but is not the MA-holder. Does the MA-holder have to have a copy of the PQR?

A: The answer is given in the full text of the EU Guidelines to Good Manufacturing Practice Part I, Chapter 1: "The manufacturer and, where different, marketing authorisation holder should evaluate the results of the review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. There should be

management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. (...) Where the marketing authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the product quality review."

The marketing authorisation holder is a key player and must have a copy of the PQR. How else could he be able to evaluate the result of this review?

Q: A contract manufacturer's QP certifies a finished product, confirming the compliance with GMP. The QP of the MA-holder makes the final batch certification, confirming compliance with the MA. If the MA-holder is outside the EU, must the contract manufacturer's QP confirm compliance with the MA?

A: Yes. Irrespective of the final release of the batch by some "QP" function outside the European Union it is the clear requirement of Article 51 of Directive 2001/83 that the QP releasing the batch in the EU has to ensure that 1. (a) "in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization;"

Usually the Technical or Quality Agreement contains an annex, describing the requirements of the marketing authorisation like manufacturing process, test methods and specifications. This is signed by both parties. Any changes and variations then have to be handled via a change control system. This ensures that the QP of the contract manufacturer always has the appropriate information.

Q: A contract manufacturer's QP certifies a finished product, confirming the compliance with GMP. The MA-holder provides artwork and labelling. What assurance should the QP of the contract manufacturer take as a minimum about compliance of artwork/ labelling with the MA?

A: There must be a Technical or Quality Agreement describing the requirements of the marketing authorisation like manufacturing process, test method and specifications. In case the contract manufacturer also performs secondary packaging, all relevant information of the packaging and labelling applying at the time of signature of the agreement must be included. This is signed by both parties. Any changes and variations have to be handled via a change control system. This ensures that the QP of the contract manufacturer always has the appropriate information.

Q: How do you perform batch record review of batches produced in China, when they are not bilingual or translated?

A: There must be a Technical Agreement and a recent audit of the company. If the company is supplying a finished drug product into the EU which needs a QP certification, a translation of one batch record as an example and a summary of each batch will be required together with a CoA. It is important that the QP can understand the process and whether there was any excursions/CAPA's /changes etc. and what they were and how they were concluded. If this was a new company to the QP, and especially if supplying parenteral drugs, I would initially want an audit at least every 12 months until the relationship was fully established.

If the company is supplying APIs, the Technical Agreement and audit requirements and ability to understand any changes/excursions will still apply. I would also want to see a copy of the process flow document together with all the critical process parameters and be able to identify these comply on a batch to batch basis together with a CoA. The companies would also need to comply with all aspects of 2011/62/EU to the satisfaction of the QP and be accompanied by a written confirmation from the competent authority of the exporting third country which confirms that the standards of good manufacturing practice and control of the plant are equivalent to those in the EU (unless a waiver has been granted).

APIs and other Starting Materials

Q: Raw material for API production: are on-site audits required for all suppliers?

A: No; however a risk based supplier quality audit programme should be established. It is important to perform a risk analysis to determine whether a supplier needs to be audited.

Q: A batch of an API has been released before all testing and final approval was completed. How do I handle this in the certification of the final product?

A: Within the EU shipment of unapproved API is not be acceptable under EU law. For shipments outside of the EU the local laws would have to be checked. It would be necessary to check what is stated in the API producer's SOP with reference to shipping unapproved material and whether that contravened any regulatory laws. The quality agreement between the API producer, the contract manufacturer and the MA holder should also be looked at to see if there is any reference to the movement of unapproved material being acceptable. It is not good practice to ship unapproved materials and as such this should have been picked up by the quality person releasing the API. Further, a deviation should have been raised and a full investigation carried out as to the root-cause. In addition the contract manufacturer should have quarantined this material on receipt and also raised a deviation to find out what went wrong. If this was a one-off incident and not a fundamental break down of the API's manufacturers and/or the contract manufacturers Quality System, then as long as the API was formally approved, you should reference the deviation report and as long as everything else was in order, certify the final drug product. However, if this incident was part of a systematic failure of the Quality System would recommend not to certify the drug product as the potential for other GMP non-conformances would be too great. The follow-up to the deviation could involve an audit of the API producer initiated by the MA holder.

Q: How far down the manufacturing supply chain (finished API – intermediate – starting materials) has the QP to place consideration when preparing a GMP API declaration?

A: Based on a risk-assessment of the process the QP must evaluate the critical materials or critical steps. The QP can base his decisions on statements of authorised persons within a QA-System.

Q: API-supplier audit: If a big company is purchasing the API in bulk and then repackaging it and doing the QC testing and release, do I as the final QP need to audit the bulk manufacturer?

A: It is the responsibility of the QP for the MAH to assure that each step in the supply chain from the starting material onwards has been manufactured in accordance with GMP. In this example it would be necessary for the final QP to either audit, or have an approved auditor carry out an audit of the bulk manufacturer. This would be in addition to having a Quality Agreement in place between the bulk manufacturer and the drug product producer.

Q: Is a QP responsible to release an API?

A: No. The EU Guidelines to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use; Part II Basic Requirements for Active Substances used as Starting Materials does not contain a reference to a Qualified Person. It is the Quality Unit that has this responsibility.

But the QP is required to confirm in an EU marketing application that the API has been manufactured in accordance with Part 2 of EU GMP. It is important to emphasise that it is the QP who is certifying the final drug product and who has to give the assurance that the API has been made in accordance with the relevant GMPs. Hence the QP must have access to appropriate documentation including supplier audits (not necessarily by the QP themselves) together with a Quality Contract (Agreement) signed by both parties, to assure her-/himself that the API does comply with the valid standards.

However, some Member States may have differing national regulations that might require QPs for certain APIs, e.g. in Germany those APIs derived from a human, animal, microbiological source, and manufactured by biotech methods.

Q: How are APIs covered under the MRA? Do APIs from non-MRA states have to be retested?

A: An API has to be re-tested on receipt no matter where it comes from. In this case the MRA is irrelevant. Testing can only be reduced or eliminated (but the ID still must be done) until the supplier has been fully qualified and has provided materials over a period of time with no issues. An on-site audit of the supplier would also have to be undertaken to ensure the supplier is meeting the required standards.

Q: What is the minimum requirement/ expectation for supplier qualification of excipients? Are on-site audits required?

A: The minimum requirement is that starting materials (including excipients and others) and packaging materials are only purchased from approved suppliers. There is no regulatory requirement for on-site audits for excipient suppliers, this is only mandatory for APIs that are manufactured under GMPs. Nevertheless, own audits or qualified third party audits or joint audits should be considered as a part of the qualification programme for suppliers and distributors of excipients besides quality and delivery history, full analysis and performance based tests.

Q: Does the manufacture and purchase of raw materials represent an activity governed by Chapter 7 of the EU GMP Guide?

A: In principle, Chapter 7 covers all outsourced activities. Therefore, the general requirements for supplier selection, approval and performance management apply equally to raw materials as to other outsourced activities. There may not be a need for Quality/Technical Agreements (QTA) with the supplier; this will depend on the nature of the arrangement between the parties. For example, if the purchaser contracts the supplier to manufacture raw materials for them, then the arrangements would need to be covered by a Quality/Technical Agreement. However, if the purchaser simply buys raw materials from the supplier a QTA would not be required.

Q: The notice to applicants requires the submission of a declaration signed by the Qualified Person (QP) that the active substance used is manufactured in accordance with GMP. The active substance in my product is widely used, but not normally as a pharmaceutical active substance, and I am having some difficulty in confirming compliance. What should I do to furnish the required declaration?

A: Full compliance with GMP for finished products and active substances is a legal obligation for manufacturing-authorisation holders. It is recognised that for a small number of medicinal products, the primary use of the active substance is not in a medicinal product and the producer may therefore not be aiming to meet the specific requirements of pharmaceutical customers that represent an insignificant volume of business. Alternative sources should normally be sought, but in exceptional circumstances the manufacturing authorisation holder should assess and document to which extent GMP is complied with and provide a risk-based justification for the acceptance of any derogation. The declaration provided by the QP should set out in detail the basis for declaring that the standards applied provide the same level of assurance as GMP. The European Medicines Agency will collect experience with this approach, which can be used as a basis for discussion on related amendments to guidelines in the future. (source: EMA Q&A).

IMP-related questions

Q: Manufacturing of tablets for a phase I and for a phase II study: is it possible to release and/or submit an IMPD or similar documentation without microbiological quality as a lot release parameters for tablets in phase I or IIa? (tablets do not contain any component that would have a high total viable aerobic count by origin).

A: Especially for IMPs manufactured the first time it should be proved that the microbial quality is satisfactory, since usually only limited experience and only little validation data are available. Although the compounds are unlikely to be "contaminated", contamination may happen during manufacturing. Often the raw materials used for the manufacture are not tested for their MB status. One approach could be to test at least the first 3 lots of a manufacturing sequence for MB status.

Independent of what is mentioned in the IMPD (and accepted by authorities), the QP keeps the final responsibility for the batch and should be able to justify her/his release decision. If the QP decides to release without MB testing, we would strongly recommend to perform a risk analysis of the release decision.

Q: Is it true and do the health agencies/ inspectorates accept that a company can import medicine from outside the EU and use it as an IMP in a clinical trial inside the EU without performing reanalysis within the EU? Is there a reference in the respective legislation?

A: That is indeed correct, Clinical trial Material (CTM) imported from a non-EU country into the EU does not need to be reanalysed/retested in Europe. This is covered in the Directive 2001/20/EC Article 13 (Manufacture and import of investigational medicinal products), at the end of paragraph 3:

"Insofar as the provisions laid down in (a), (b) or (c) are complied with, investigational medicinal products shall not have to undergo any further checks if they are imported into another Member State together with batch release certification signed by the qualified person"

In this article the QP certification act is described as well. In summary it mentions that the QP should certify that the CTM is compliant with:

- European (or equivalent) GMPs
- The product specification file
- The IMPD (Investigational Medicinal Product Dossier)

Remark:

-the IMP QP can always decide to reanalyse/ retest the imported CTM. Important to know is that this is not mandated by the EU HAS.

Q: Should a QP audit CROs and investigators or can a QP rely on GCP-auditors of the own company?

A: The QP can rely on the information provided by the GCP auditors.

Q: When IMPs are imported from outside the EU; how could I set up a working relationship as a contract QP when it comes to liability and insurance?

A: As a contract QP you are a "normal" contracting party (i.e. just like any other service provider for the company but with the specific legal responsibilities and risks of a QP) and therefore no employee of the company. That means that you are not covered by any of the insurance programmes which companies usually provide for their employees (e.g. D&O insurance). As a result, you should mention that fact – and the related legal risks – during your contract negotiations with the company.

Ideally, there should be an indemnification clause in the service contract providing for that 'the company indemnifies the contract QP from any and all third party claims related to the services which the contract QP may perform under the service contract'. If your current contract does not contain such provision, you should ask the company to sign an amendment with aforesaid clause.

You can also ask the company to get yourself explicitly included in its D&O insurance contract (some insurers may actually be ready to do so because of the specific situation of the contract QP). This inclusion could be the first part of the contractual provision, followed by the indemnification clause mentioned above.

3.5. Good Distribution Practices (GDP)

1. General Questions & Answers on Good Distribution Practices (GDP)

Is it necessary for a manufacturer of medicinal products to comply with the Good Distribution Practices (GDP) or is this the task of the wholesalers and distribution companies?

>> GDP requirements are very similar to the requirements stated in the GMP for manufacturers in relation to storage of medicinal products. Manufacturers must comply with the product storage requirements as stated in the GMP. In addition, if they are responsible for the distribution of their products, they also need to follow the GDP requirements; these include storage and transportation of their products in line with the product label, ensuring its safety and security throughout the supply chain.

According to Chapter 2, paragraph 2.2. each wholesaler needs to designate a person as Responsible Person for GDP. Are there any circumstances in which the manufacturer of the medicinal product needs to designate a Responsible Person?

>> The EU Manufacturing authorization includes the wholesaler's license, therefore a manufacturer can legally distribute its products, the QP named in the Manufacturing License can take the responsibility for storage and distribution of the product. As a consequence, there is no need for the manufacturer to name an RP. However, depending on the organization structure and the complexity of the operation, the company may appoint a person responsible for product distribution.

Each Wholesaler needs an authorization issued by the competent authority of the Member State where the wholesaler is located. Are there any authorizations needed for a warehouse/storage facility?

>> Yes, if a product is stored in a storage facility this facility should be included in either the manufacturers' (Manufacturing License) or the wholesaler's license. In the EU, you cannot store products in an unlicensed facility (except at the distribution hub for short durations, e.g. 24 hrs)

Each manufacturer of a medicinal product needs to control and supervise the supply chain (wholesaler, transport and distribution companies etc) of the finished products. Is this in the responsibility of the Qualified Person of the manufacturer of the medicinal product?

>> The Owner of the product in the supply chain is responsible for its management in the supply chain, if the manufacturer owns the product in the supply chain, then their QP is normally responsible for the product in the supply chain. Of course this responsibility can be delegated to another QP or an RP, but the ultimate responsibility will remain in the hands of the product QP.

I've heard about a requirement that medicinal products should not be stored for more than 24 hours because in that case the facility would need to have a licence. What is the reference for this requirement?

>> Chapter 9 of EU GDP (Last Paragraph) states 'Provision should be made to minimize the duration of temporary storage while awaiting the next stage of the transportation route' this duration should be specified in companies SOPs based on risk assessment. The current industry practice is 24-72 hours storage at temporary facilities. Longer storage periods are classed as long term storage of product and the facility must have a licence to operate.

As a manufacturer of finished medicinal products, do I need to audit all transport organisations, all warehouses and all wholesalers who will handle my products? What about transportation hubs e.g. at airports. There might be hundreds of such facilities.

>> The Current EU GDP requires manufacturers to have audited and approved all their outsourced activities and have a technical/quality agreement with their service providers. The approach to selection and approval of these facilities should be supported by risk assessment, companies can use shared audits or 'paper audit' depending on the complexity of operations and sensitivity of the products involved.

3. Questions & Answers about the Scope of the GDP Guideline

1) Does the EU GDP Guide cover both Human Medicinal Products and Veterinary Medicinal Products? The full text of the EU GDP Guide provides the answer: Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use (2013/C 343/01). This means Veterinary Products are not covered but it might be useful to adopt GDP principles based on a risk assessment on a voluntary basis.

2) Does the EU GDP Guide cover Investigational Medicinal Products (IMPs) and Radiopharmaceuticals? The GDP Guidelines focus on wholesale distribution of medicinal products. And IMPs are normally not distributed via wholesalers. However IMPs are not particularly excluded. The Guideline may therefore give some guidance on how to supply clinical trial material. More detailed guidance might be given by the Questions and Answers section of the European Medicines Agency. In the part on supplementary requirements, Annex 13 a few Q&As are dealing with storage and transportation of IMPs.

Radiopharmaceuticals are Medicinal Products and therefore within the scope of the EU GDP Guideline. The GDP Guideline contains a reference to them: "Medicinal products comprising highly active and radioactive materials should be transported in safe, dedicated and secure containers and vehicles."

3) Are there any GDP requirements for APIs and Excipients in place? Good Distribution Practice of Active Pharmaceutical Ingredients (APIs) is covered in a separate Guideline. The requirements can be found in: Guidelines of 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use. These requirements are legally binding in Europe. For Excipients there is no such regulation in Europe. However, an industry standard exists and should be applied on a risk based approach: IPEC Good Distribution Practices Guide for Pharmaceutical Excipients.

4) Is Transportation covered by the EU GDP Guide and can Transport companies receive a GDP Certificate?

This question has been addressed by the EU Commission in a Q&A paper: "Transport companies do not need to hold a wholesale distribution authorisation to transport medicinal products. However, they should follow the parts of the GDP guideline relevant to their activities, amongst others Chapter 9." Therefore Transport companies need to follow GDP but will not receive a GDP certificate. GDP should be assessed by the customers who ship medicinal products with certain transport companies.

5) Who does issue a GDP Certificate?

The so called competent authorities in Europe have to issue the GDP certificate. Please find here a list of the competent authorities. The details (including the exact procedure and documentation) of the GDP Inspection and Certification is defined in the EMA/EU Commission: Compilation of Community Procedures on Inspections and Exchange of Information.

According to the document: "The contents of the initial inspection report should be sent to the company for its comments to enable the report to be finalised within the relevant timeframe of the inspection request and to enable, if applicable, the issue of a GDP certificate within the statutory 90-day timeframe..... The GDP certificate or the non-compliance statement shall be entered in the Union database referred to in Article 111(6) of Directive 2001/83/EC.....The intervals between inspections should be set at a level that provides confidence that the wholesale distributor maintains continued compliance with GDP and its principles. The maximum period between inspections per site should not exceed 5 years as lack of continuity may give rise to lower awareness of current GDP or allow significant deficiencies to develop".

6) Are Transport Hubs covered by EU GDP?

Hubs are sometimes needed to store goods for a short time period, e.g. in order to collect goods for further shipment. Hubs can be found at airports and usually store products between 24 and 72 hours. They are not intended to store products for a longer time. Chapter 9 of EU GDP (Last Paragraph) states: Provision should be made to minimize the duration of temporary storage while awaiting the next stage of the transportation route. This duration should be specified in companies' SOPs based on risk assessment. The current industry practice is 24-72 hours storage at temporary facilities. Longer storage periods are classed as long term storage of product and the facility must have a licence to operate. This means that Hubs will not have a GDP certificate but will need to comply with EU GDP based on a risk assessment.

3. Question & Answers on Chapter 1 QUALITY MANAGEMENT of the EU Good Distribution Practice Guideline

1) Chapter 1 requires a Quality System. Is a Quality System according to ISO 9001 and the certification appropriate to comply with the requirements?
ISO 9001, is a generic quality management system providing a good framework for any organisation. However, the EU GDP expectations are not clearly detailed in this standard. It is therefore recommended that companies using the ISO framework incorporate the specific GDP requirements to ensure a compliant and workable QMS is available for the company. It is worth noting that the EU GMP and GDP both have been designed around the structure of the ISO9001. In simple terms ISO 9001, certification is not sufficient to meet the GDP licencing requirements. It is important that a Quality System is designed to identify and supervise all distribution activities of the medicinal product. The Quality System should be designed to assure the quality of the medicinal products at all levels of the supply chain.

2) What are the key requirements for a Quality System which is demanded by the EU GDP Guide? Some key aspects are mentioned in section 1.2:

- (i) medicinal products are procured, held, supplied or exported in a way that is compliant with the requirements of GDP;
- (ii) management responsibilities are clearly specified;
- (iii) products are delivered to the right recipients within a satisfactory time period;
- (iv) records are made contemporaneously;
- (v) deviations from established procedures are documented and investigated;
- (vi) appropriate corrective and preventive actions (commonly known as 'CAPA') are taken to correct deviations and prevent them in line with the principles of quality risk management.

Also the control of outsourced activities, and Quality Risk Management should be an essential part of the Quality System. In general, the Quality System should have written procedures e.g. in the Quality Manual and in SOPs about how each requirement in the 10 Chapters of the EU GDP Guide will be implemented in the company.

3) In the Supply Chain many logistic activities are outsourced to service providers e.g. transport and storage. Is it possible to agree a contract with the service providers so that they will be solely responsible also for the quality system and the quality of the medicinal product?
No, the responsibility for the compliance with the GDP requirements as well as for the quality of the medicinal product will always remain with company who wants to outsource certain services to a service provider (i.e. the WDA holder). Moreover, the company and its Responsible Person is also responsible for all services which might be outsourced by the service provider. This will help ensure that subcontracting will not cause additional risks to the products. It is recommended in these situations to have a quality agreement in place that defines duties and responsibilities between outsourced service providers and WDA holders. Both must have implemented a quality system that complies with GDP requirements. In principle the same requirements will apply for outsourced activities as for internal processes. This is why outsourced services should be covered in an internal audit programme as described in Chapter 8 (Self-Inspection). Chapter 7 deals only with outsourced activities and what is needed in detail to comply with the GDP Guide. A key component of the Quality System is detailed contracts with every company who takes over the defined activities. These contracts and the compliance with the contracts should be monitored as part of the Quality System of the Contract Giver.

4) According to Chapter 1.5 a Quality Risk Management should be in place. What is required also with regard to the necessary documentation?

Quality Risk Management is a fundamental part basis of a GDP-compliant Quality System. Application of risk management techniques will identify potential high risk areas in the business allowing the management to take appropriate preventive action to protect the business as well as the customers of the company. It also helps reduce wasting resources on low risk areas. Chapter 5 contains a reference to ICH Q9, a Guideline dealing with Quality Risk Management for Medicinal Products. It is recommended using this Guideline when developing and implementing a Quality System. The EU GDP provides several examples where a risk management tools can be applied: For example:

- 3.2.2. Temperature and environment control: The mapping exercise should be repeated according to the results of a risk assessment exercise or whenever significant modifications are made to the facility or the temperature controlling equipment.
- 3.3. Equipment: Equipment used to control or to monitor the environment where the medicinal products are stored should be calibrated at defined intervals based on a risk and reliability assessment
- 3.3.2. Qualification and validation: The scope and extent of such qualification and/or validation activities (such as storage, pick and pack processes) should be determined using a documented risk assessment approach.
- 5.1. Operation – Principles: The wholesale distributor should use all means available to minimise the risk of falsified medicinal products entering the legal supply chain.
- 6.3. Returned medicinal products: Returned products must be handled according to a written, risk- based process taking into account the product concerned, any specific storage requirements and the time elapsed since the medicinal product was originally dispatched.
- 9.2. Transportation: Risk assessment of delivery routes should be used to determine where temperature controls are required.

4. Questions & Answers on Chapter 2 of the EU Good Distribution Practice Guide **The answers are made by using the PQG/ECA Interpretation Guide on GDP**

1) According to Chapter 2, paragraph 2.2. each wholesaler needs to designate a person as Responsible Person for GDP. Are there any circumstances in which the manufacturer of the medicinal product needs to designate a Responsible Person?

The EU Manufacturing authorization includes the wholesaler's license, therefore a manufacturer can legally distribute its products, the QP named in the Manufacturing License can take the responsibility for storage and distribution of the product. As a consequence, there is no need for the manufacturer to name an RP. However, depending on the organization structure and the complexity of the operation, the company may appoint a person responsible for product distribution.

2) Chapter 2, paragraph 2.2 requires that the responsible person should have appropriate competence and experience as well as knowledge of and training in GDP. A degree in pharmacy is desirable. If a RP is not a pharmacist what qualification may be accepted by authorities?

The appointment of a RP must be carefully considered to ensure to the correct person is put in place. This appointment is dependent on the size of the organisation, the complexity of the services to be provided and the product classes to be supplied. The nominated responsible person should be able to show an in-depth understanding of medicinal products and must be able to demonstrate knowledge of GDP, and how it is imbedded within the systems and processes implemented within the wholesale distributor. Some key areas of knowledge and experience are listed below:

Knowledge

- Storage conditions/requirements for different types of pharmaceutical product;
- Basic understanding of degradation pathways and stability profiles of pharmaceutical products;
- GDP legislation and relevant guidance;
- Requirements for storage facilities, temperature control and monitoring programmes, including mapping and qualification;
- Quality Management Systems and how to manage these effectively;
- Handling of returns/complaints/recalls;
- Bona Fide checks;
- Risks associated with Falsified Medicines;
- Expectations of a robust Technical (Quality) Agreement with any sub-contractors;
- Controlled Drug legislation and requirements of the relevant Member State(s);
- Trained auditor.

Experience

- Experience of picking /packing procedures and FEFO (First Expiry, First Out) principles;
- Handling complaints and customer queries;

- Active involvement in GDP regulatory inspections;
- Audited internally to monitor the Quality Management System (QMS) and preferably also external audits covering the various stages in the distribution process;
- Supplier and Customer approval process;
- Creating/maintaining/auditing the documentation and records involved to ensure compliance with GDP.

3) What are the key elements which should be covered a job description for Responsible Person?

The following objectives and responsibilities should be covered in the job description:

- The RP should ensure that a QMS is implemented and maintained;
- He/she should focus on the management of authorised activities and the accuracy and quality of records;
- The RP should ensure that initial and continuous training programmes are implemented and maintained;
- He/she should be responsible for coordinating and promptly performing any recall operations for medicinal products;
- The RP should ensure that relevant customer complaints are dealt with effectively;
- The RP should ensure that suppliers and customers are approved;
- The RP should approve any subcontracted activities which may impact on GDP;
- The RP should ensure that self-inspections are performed at appropriate, regular intervals following a prearranged programme and necessary corrective measures are put in place;
- He/she should keep appropriate records of any delegated duties;
- The RP should decide on the final disposition of returned, rejected, recalled or falsified products;
- He/she should approve any returns to stock;
- The RP should ensure that any additional requirements imposed on certain products by national law are adhered to.

An example of a job description can be found in the Code of Practice for RPs which has been published by the GDP Association. You can download the document in the Members Area (if you are not a member yet you can apply for free membership [here](#)).

4) Chapter 2, paragraph 2.4 requires that all personnel involved in wholesale distribution activities should be trained on the requirements of GDP. They should have the appropriate competence and experience prior to commencing their tasks. How can this be achieved in practice?

It is the responsibility of senior management in conjunction with the RP to ensure that the initial and continuous training of personnel is implemented. The RP should have direct input into the design and implementation of a GDP induction programme for all personnel. This should be based on the job description and the level of detail should reflect the position of responsibility within the QMS and organisation as a whole.

The induction training should be captured in a procedure and clearly outline the minimum requirements and tasks which may consequently be performed. It should also include details of the approval process.

Subsequent training in GDP should be planned and cover greater detail. This must be captured in the overall training programme for the organisation. Mechanisms must be in place to ensure that persons not yet trained in GDP are not allowed or asked to complete any relevant tasks. This relies on good management oversight of the training programme and matrix for their direct reports. It also relies on personal integrity of individuals to resist the temptation to complete tasks for which they have not been inducted or trained and the training programme should emphasise this.

5) Chapter 2 requires a written training programme. What does this mean in practice?

The overall training programme is often captured in a training matrix. This method is effective and can be tailored to roles and departments. Training frequency and results of competency tests can also be captured along with prompts for retraining. A simple Excel spreadsheet can be effective providing it

is regularly maintained and reviewed. Training should be clearly split into stages tied with activities that may or may not be consequently performed by the individual.

Training processes can be split into 4 stages:

1. Training needs identification
2. Training guides developed (SOPs)
3. Training implementation
4. Training outcomes evaluation

More details about the 4 stages can be found in the PQG/ECA Interpretation Guide on GDP. You can download the document in the Members Area (if you are not a member yet you can apply for free membership [here](#)).

5. Questions & Answers on Chapter 3 of the EU Good Distribution Practice Guide (Premises and Equipment)

1a) Segregation of different materials: Which products can be stored in the warehouse with segregation based on a computerised system? And which products do need physical segregation?

Segregation based on a computerised system is possible for:

- Products pending a decision as to their disposition
- Products that have been removed from saleable stock
- Product suspected of falsification
- Returned products

Physical segregation is mandatory for:

- Medicinal products received from a third country and not intended for EU market
- Falsified medicinal products
- Expired products
- Recalled products
- Rejected products

Some regulatory authorities in the EU Member States might have differing perspectives on this point, so it is important to understand specific national requirements.

1b) What are the pre-requisites for segregation based on a computerised system?

Computerised (electronic) segregation is accepted where validated to provide appropriate security. Personnel with access to electronic systems must have unique user identifications and passwords to allow clear traceability of actions taken. Staff access within electronic systems should be tied to the functionality that they require to perform their job. The ability to change material status should be limited to the Responsible Person or a designate. An IT policy should be in place for the management of system access and passwords in line with EU GMP Annex 11, Section 12.

1c) What are the pre-requisites for the area for physical segregation?

A dedicated and clearly identified area is needed. Access to these areas must be managed with restriction to authorised personnel only. An appropriate degree of security should be applied in these areas to ensure that products remain separate from saleable stock. Storage areas for controlled substances must be segregated and physically secure in accordance with national legislation.

2) How can receiving and dispatch bays be designed to protect products from prevailing weather conditions?

Protection from adverse environmental conditions can be achieved via a combination of an external canopy, vehicle tunnels, appropriate doors and procedures during receipt and dispatch. The facility should be designed and operated with logical product flow reflected by clear signage and floor markings in place to identify separate inbound/outbound areas. It should be ensured that adequate space and lighting is available for all activities.

3) For premises and storage facilities, adequate cleaning programmes should be in place. How can this be realised?

The cleaning regime should be systematic, covering all areas, including racking, on an appropriate frequency to maintain cleanliness. The respective process should be defined in writing based on a risk assessment evaluating all relevant factors and conditions. Checklists may be useful. Cleaning procedures should also cover the handling of spillages.

Cleaning equipment should be kept clean and dry and periodically replaced. Cleaning agents need careful selection to ensure that products are not damaged by chemical reaction or tainted by odour. Disinfectants and cleaning agents should be specified in procedures and no other agents allowed to be used. All cleaning activities should be recorded (log file).

The effectiveness of cleaning should be assessed as part of the self-inspection programme. Periodic checks for fungal/mould growth should be made, especially in cold stores.

4) What is an adequate preventive pest control programme?

The pest control procedure should include:

- Site plan
- Location of different pest control measures (e.g. bait boxes, ultraviolet insect killers)
- Frequency of inspections
- Review of reports

Pest control agents should be selected to avoid the risk of contaminating products. Many companies use licensed pest-control experts or a pest control service. A contract should be in place to cover such work.

5) Can I take personal medication into the storage area?

Requirements for personal medication should be risk based. Generally, medication should be kept in lockers and not taken into storage and distribution areas. However exceptions may be appropriate, e.g. allowing asthmatics to carry reliever inhalers with them.

6) Where should we put temperature monitoring equipment?

Warehouse temperature monitoring should be based on a mapping exercise which has identified the worst case positions.

Ideally, the first mapping exercise should be carried out before a storage area is used (this may not always be possible, e.g. in the case of an existing warehouse already in use). Once the initial mapping has been completed, the data should be assessed and used to determine where the most suitable locations for monitoring devices are. These are typically locations seen to have experienced the largest temperature fluctuations. A second exercise should be carried out once the facility has been approved and product is in place. Repeat exercises should then be carried out based upon the results of a risk assessment considering also seasonal weather variations.

7) What is "key equipment" which needs planned maintenance and qualification activities?

This is basically all equipment that may have an impact on product quality. Examples of this equipment are: HVAC systems, alarms, measuring equipment etc. For those facilities performing labelling operations these are also: printers, bar code scanners, etc.

8) What is needed for a sound validation of computerised systems?

All computerised systems with a potential to impact product quality within the facility should be identified by risk assessment.

Steps in the validation process include:

- URS (User Requirement Specification) to document what is expected from the system,
- DQ (Design Qualification),
- IQ (Installation Qualification),
- OQ (Operational Qualification),
- PQ (Performance Qualification).

Controls and access rights should be defined and implemented. All changes should be subject to a formal change control process.

A Business Continuity Management Plan should exist to cover the event of IT system failure. Regular backups of IT systems should be performed.

6. New: Questions & Answers on Chapter 4 of the EU Good Distribution Practice Guide (Documentation)

1) Who authors documents? Who needs to approve them?

Instruction documents (Procedures, and work instructions) should ideally be written by the subject matter experts and reviewed and approved by the management and QA/RP. Forms for recording data, e.g. check lists; reports; weight recordings; bar code readings etc. should be developed as part of the relevant SOPs by the SOP authors.

The forms should be used to record data directly by the user during each relevant activity. This will minimize the risk of errors as there is no need to rely on memory or the transcription of data from unofficial records e.g. from a personal notebooks or on pieces of paper onto the forms at a later time point. Depending on the type and definition of the activity there may be a need for a second checking/verification of the data entered, performed by another authorized/trained person. The EU-GDP Guidelines chapter 4 require that procedures are approved (signed and dated) at least by the Responsible Person (RP). Other documentation (none GDP) should be approved, signed and dated by appropriate authorised persons, as required. The approval of the procedures by the Responsible Person ensures that he/she has full oversight of the quality system ensuring its fitness for purpose. Signing and dating documents ensures that there is clarity regarding who performed the activity and when (traceability). Note that signing and dating may be by electronic means as well as 'pen on paper'. If electronic signature is used, then the system providing this should have been validated in line with the requirements of validation of the electronic system in the EU GMP, Annex 15.

2) What needs to be considered when handling personal data?

Some GDP-relevant documents may fall within the scope of European Union legislation designed to protect individuals' right to privacy and there are penalties for infringements. It is therefore important that systems are in place for the compliant handling of such data. Staff members need to be aware of the applicable data protection legislation and trained in use of the company data handling systems. See: DIRECTIVE 95/46/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

3) In which language should documents be written?

Since the documentation system, comprising both instructions and records, is fundamental to the quality system, it needs to cover the full scope of operations. These documents exist for the benefit of personnel and therefore need to be in a language understood by them.

4) Why should documents be kept for at least five years?

The minimum duration of five years aligns with the maximum shelf life accepted by the European Medicines Agency for a marketed medicinal product for human use. However, national legislation may exceed this (e.g., six or seven years) providing an additional period after the expiry date.

5a) Are paper copies allowed, e.g. for procedures and/or work instructions?

Yes, especially in the absence of electronic systems. Procedures and work instructions need to be followed at all times; therefore they might need to be located in the workplace as paper copy, if electronic access is not practicable. Sometimes it is even necessary: it enables operators to enter information directly onto the formal paper record at the time an activity takes place, not writing information onto pieces of paper for transcription later increases the risk of data being lost or errors being made.

If paper records are made, specific locations in each work area should be provided where these can be safely and conveniently kept while operations are in progress. Superseded procedures must be removed from workstations to avoid their inadvertent use. Therefore these documents should be uniquely numbered or coded with effective date, revision date and version number.

5b) Is it allowed to print procedures from an electronic system?

Yes, but it is important to ensure staff do not keep personal printouts of superseded versions. Training in a new version should include a reminder about this and checks should be carried out at least during self-inspections. Consideration should be given to preventing printing if it can be assured that staff will have access to terminals at point of operation. The printed copies should be clearly identified as a copy valid on the day it was printed. It is recommended that staff are trained to destroy any printed copy of procedures at the end of the day to avoid risk of using/referring to older version of documents.

7. New: Questions & Answers on Chapter 5 of the EU Good Distribution Practice Guide (Operations)

1) What needs to be considered when importing medicinal product from outside the EU?

If products are to be sourced from outside the EU, then the importer must have a Manufacturing Importation Authorisation (MIA) obtained from the local authorities before commencing any importation of medicines. The scope of this license is outside the GDP guidelines the importer should have access to services of a QP, and comply with the appropriate GMP regulations.

2) How can I check if a supplier has an appropriate legal authorisation?

The use of the EudraGMDP database is recommended which contains details of the majority of the current Wholesale Distributor Authorisations (WDA) holders in EU and the GDP certificates for those companies have been audited by the authorities. The database also includes non-compliance reports of the companies who have failed inspections. (note: not all certificates are available yet):
<http://eudragmdp.ema.europa.eu/inspections/displayHome.do>.

Registers of brokers are maintained by the national competent authorities. However not all member states currently publish such a list.

In addition to using the EudraGMDP database, the supplier should be asked to provide you with a copy of their authorisation (as per local procedures). This document should be verified.

In some member states there are additional information regarding pharmacies, hospital and clinics which are authorized to receive certain types of medicinal products, it is recommended you check availability of such information in your country.

3) Why do I need to qualify customers?

EU-GDP requires that "Wholesale distributors must ensure they supply medicinal products only to persons who are in possession of a wholesale distribution authorisation or are authorised / entitled to supply medicinal products to the public" (5.3)

By ensuring supply to the authorised companies, wholesale dealers help to maintain a reliable 'chain of custody' to the patient and reduce the risk of products being misdirected and/or misused.

4) Besides temperature, are there other environmental factors which might harm medicinal products?

Yes!

Light: Packaging normally provides appropriate light protection, but issues can still be caused by exposure to strong artificial light sources or sunshine resulting in localized heating of the product or discoloration of the packaging and labels.

Moisture: If products are exposed to vapour or high humidity then they can be susceptible to hydrolytic degradation or physical deterioration. As with light, product packaging systems, normally design to protect the product from environmental humidity, however, there is always a risk to the packaging components (cartons and labels) from high humidity in storage. Damage to cartons/labels from high humidity include discoloration, destruction of cartons, and buildup of mold. **Vibration:** Rocking motion or vibration could lead to segregation of powders and suspension or breaking of glass components.

Others: These could include strong odours or spilled chemicals which could have direct impact on products or their packaging rendering them unsuitable for use.

5) What is the meaning of FIFO and FEFO?

FIFO = "first in, first out"; it means that products stored first are to be retrieved first.

FEFO = "first expiry, first out"; this is to ensure that product with shortest expiry date is placed into the market first. It also helps to ensure that products reaching end users have sufficient remaining shelf life.

EU-GDP prefers FEFO principle. Exceptions are possible but "should be documented/justified".

6) Why is it not allowed storing product directly on the floor?

Products stored on the floor are more likely to become damaged or contaminated by spillages, water, dirt and or pests.

7) Why do I need to document the destruction of obsolete drugs?

This ensures that these products do not inadvertently (re-)enter the supply chain or become diverted.

4 FDA (USA)

4.1. General Provisions

1. Are USP general chapters above <999> considered equivalent to FDA guidance? What is their purpose and how should manufacturers use these informational chapters?

No, FDA is the only source of policy on pharmaceutical CGMPs and quality. CGMP requirements are found in statutes and regulations, and FDA's current thinking on these requirements is explained in the Agency's guidance documents.

The U.S. Pharmacopeial Convention is a private, nongovernmental organization that publishes the United States Pharmacopeia (USP) and the National Formulary (NF) as official compendia of the United States. Although much of the USP and NF is legally enforceable, the USP general chapters numbered above <999> (general information chapters) are informational and generally do not contain any mandatory requirements (see USP General Notices 2.10). General information chapters might include some recommendations that may help a firm meet CGMPs.

References:

- [Federal Food, Drug, and Cosmetic Act](#)
- [United States Pharmacopeial Convention](#)

Date: 6/14/2007

2. How does one comment on FDA's proposed guidance documents? How about USP proposals?

Both USP and FDA have mechanisms in place for interested parties to make comments on proposed documents.

1. Guidance Documents

FDA's proposed guidance documents are written using good guidance practices and published for comment per 21 CFR 10.115. They are easily accessible to the public via our Web site and through the [Federal Register](#). FDA's Division of Dockets Management is the office responsible for receiving all comments on proposed guidance. Interested parties can read and submit comments via FDA's [Dockets Management Web site](#). FDA reviews all received public comments, makes appropriate modifications, and publishes a final document.

2. USP Monographs

USP publishes proposed chapters or monographs in the *Pharmacopeial Forum*, a publication that is issued bimonthly. USP subscribers have access to these publications and can send comments (within a 90-day post publication comment period) for consideration by the USP. Finalized proposals (official revisions, new chapters, or monographs) are published in subsequent supplements to or editions of the Pharmacopeia.

References:

[United States Pharmacopeial Convention](#)

Date: 4/30/2009

4.2. Building and Facilities

1. What is Penicillin?

Penicillin is defined as a group of natural or semi-synthetic antibiotics derived from fungi strains of the genus *Penicillium*. Generally, all penicillins share a three-carbon, one-nitrogen, and four-member cyclic amide structure, known as the beta-lactam ring.

Reference:

- Lewis, J, and K Bush, 2015, Antibacterial Agents, In: J Jorgensen, M Pfaller, K Carroll, G Funke, M Landry, S Richter, D Warnock, eds. Manual of Clinical Microbiology, 11th ed., Washington, DC: ASM Press, 1171-1211.

Date: 6/29/2009

2. What are the Penicillin drugs?

The Manual of Clinical Microbiology, 11th edition, identifies penicillin drugs as follows:

Natural

- Benzylpenicillin (penicillin G)*
- Phenoxymethyl penicillin (penicillin V)*

Semisynthetic

Penicillinase resistant:

- Cloxacillin*
- Dicloxacillin*
- Nafcillin
- Oxacillin
- Temocillin**

Extended spectrum:

- Aminopenicillins
 - Amoxicillin*
 - Ampicillin*
 - Mecillinam**
- Carboxypenicillin
 - Ticarcillin*
- Ureidopenicillin
 - Piperacillin

*Approved for veterinary use

**Not approved in the United States

Please be aware that penicillin trade names may vary by region and country. Manufacturers, including repackers, are responsible for knowing whether their drug is penicillin. FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) or Drugs@FDA, both of which are located on FDA's [Web site](#), enable searching by trade name (i.e., proprietary name) and by active ingredient name (i.e., generic or non-proprietary name).

References:

- Lewis, J, and K Bush, 2015, Antibacterial Agents, In: J Jorgensen, M Pfaller, K Carroll, G Funke, M Landry, S Richter, D Warnock, eds. Manual of Clinical Microbiology, 11th ed., Washington, DC: ASM Press, 1171-1211.
- [FDA Orange Book](#)
- [Drugs@FDA](#)

Date: 6/29/2009

3. Is cross contamination a concern with Penicillin drugs?

Yes, penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people. Differences in the chemically substituted 6-aminopenicillanic acid side chain can generate allergic reactions ranging from skin rashes to life-threatening anaphylaxis.

Reference:

- Lewis, J, and K Bush, 2015, Antibacterial Agents, In: J Jorgensen, M Pfaller, K Carroll, G Funke, M Landry, S Richter, D Warnock, eds. Manual of Clinical Microbiology, 11th ed., Washington, DC: ASM Press, 1171-1211.

Date: 6/29/2009

4. Are there special manufacturing requirements for Penicillin drugs?

Yes, all penicillin finished pharmaceutical manufacturers, including repackers, are required by the CGMP regulations to establish a comprehensive control strategy designed to prevent cross contamination of other drugs with penicillin. These requirements include:

- 21 CFR 211.42(d): Separation of facility and equipment

- 21 CFR 211.46(d): Separate air handling systems (HVAC)
- 21 CFR 211.176: Test for traces of penicillin where possible exposure exists.

Penicillin active pharmaceutical ingredients (APIs) are also required to be manufactured under CGMPs in accordance with section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. FDA has published internationally harmonized guidance on the manufacture of APIs; see ICH guidance for industry, *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. Chapter 4, section 4.4 of this guidance describes actions API manufacturers, including those that manufacture or package APIs or penicillin intermediates, are to follow to ensure such material is contained and does not contaminate other drugs.

References:

- [FDA CGMP regulations](#) (21 CFR parts 210–211)
- [Federal Food, Drug, and Cosmetic Act](#), section 501(a)(2)(B)
- FDA Guidance for Industry, 2001, [ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients](#)

Date: 6/29/2009

5. Why is FDA concerned about drug contamination with halogenated anisole compounds, such as 2,4,6-tribromoanisole (TBA)?

Reports, including some dating back several decades, describe a moldy or musty odor in food (and wine) products due to contamination with trace amounts of halogenated anisole compounds such as 2,4,6-tribromoanisole (TBA). An odor attributable to the presence of a halogenated anisole compound can be detected by consumers even when the offending compound is present at parts per billion or lesser levels. An upward trend in consumer complaints about musty or moldy odor led a drug firm to identify TBA as the odor-causing compound. The firm's investigation of this incident led to the detection of TBA in several oral products. The firm traced all of the contamination back to the use of certain wooden pallets used to transport drug packaging materials. TBA is prone to volatilize and adsorb onto articles stored near the TBA source. Because of their volatility, it appears that even minute levels of halogenated anisole compounds can adversely affect a large quantity of product in a single contamination incident.

Date: 3/12/2010

6. Are there any health effects associated with ingestion of halogenated anisole compounds?

Although there is no meaningful toxicological data on TBA at these levels, the health risks appear to be minimal. Currently available data indicate that serious adverse health effects have not resulted from ingestion of drugs or foods contaminated with halogenated anisole compounds at the levels of contamination that have been reported. However, there are some reports of gastrointestinal events by consumers who also report sensing a foul odor, or taste, in drug products contaminated with the typical trace levels of TBA. Even if the health effects are minimal, FDA is concerned that patients sensing an unusual odor that is not intrinsic to the product will stop taking their medication.

Date: 3/12/2010

7. Has FDA identified the source of the halogenated anisole compounds that have contaminated drug products?

The source of TBA-contaminated drug products appears to have been 2,4,6-tribromophenol (TBP), a chemical used as a wood preservative. Certain fungi are able to survive in TBP-treated wood by converting TBP to its anisole analog, TBA.¹ In the contamination incident, an investigation found that TBP-treated wood was used to manufacture pallets that were then used to ship and store drug packaging material. Currently, the use of halogenated phenolic compounds to preserve wood appears to be very rare as this practice is either discouraged or prohibited in many regions of the world,

including the United States. However, TBP treatment of wood continues in some regions that supply wood to the United States and other countries.

¹Trichlorophenol (TCP) is another example of a compound that can be converted to a halogenated anisole compound.

Date: 3/12/2010

8. What is FDA's expectation for preventing contamination of drug products with halogenated anisole compounds?

FDA recommends that manufacturers and distributors take precautions to prevent the use of wood products treated with or exposed to a halogenated phenolic preservative anywhere in the supply chain. This includes all facilities that manufacture, hold, or distribute drug products, components, or packaging materials. We recommend that manufacturers not store drug products, components, or packaging materials near wood or wood-derived storage materials unless there is assurance that the wood material has not been treated with a halogenated phenolic preservative.

FDA further recommends that manufacturers establish agreements and request certification from suppliers to provide assurance that halogenated phenolic preservatives are not present. Manufacturers should also be vigilant to the characteristic odor of the offending compounds so they can intervene before products are contaminated or further distributed.

Date: 3/12/2010

9. Are there any standards applicable to preventing contamination of drug products with halogenated anisole compounds?

U.S. (ASTM) and international standards (International Standard for Phytosanitary Measures (ISPM)) recommend heat treatment, or fumigation with methyl bromide, for the preservation of wood-derived packaging storage materials, including wood pallets. For more information, including certification to these standards, refer to Standard Practice for Treatment and/or Marking of Wood Packaging Materials (ASTM D 6253-10) and Guidelines for Regulating Wood Packaging Material in International Trade (ISPM 15).

References:

- ASTM Standard D6253-10, 2010, Standard Practice for Treatment and/or Marking of Wood Packaging Materials, West Conshohocken, PA: [ASTM International](#)
- ISPM 15, 2013, Guidelines for Regulating Wood Packaging Material in International Trade, Rome: [Secretariat of the International Plant Protection Convention of the Food and Agriculture Organization of the United Nations](#)

Date: 3/12/2010

10. Can contamination of drug products with halogenated anisole compounds be detected?

Although methods for detection exist and might be practical for periodic screening, FDA expects that manufacturers prevent such contamination through adherence to CGMPs. A CGMP-compliant quality system will ensure that assurances are obtained from suppliers and that measures are taken to prevent exposure to problematic compounds. Manufacturers of finished pharmaceuticals are reminded that the CGMP regulations at 21 CFR 211.56(c) require written procedures for sanitation designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, and drug products. Analogous recommendations for manufacturers of active pharmaceutical ingredients are included in internationally harmonized (European Union, Japan, United States) ICH guidance for industry *Q7 Good Manufacturing Guidance for Active Pharmaceutical Ingredients* (section 4.7).

References:

- 21 CFR 211.56: [Sanitation](#)

- [FDA CGMP regulations](#) (21 CFR parts 210–211)
- FDA Guidance for Industry, 2001, [ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients](#)

Date: 3/12/2010

Contact for further information: CDER-OPQ-Inquiries@fda.hhs.gov

4.3. Equipment

1. Many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be?

The auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check (21 CFR 211.68). For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step. Note that all batches of a product manufactured between two successive verifications would be affected should the check of the auto-calibrator reveal a problem. Additionally, the calibration of an auto-calibrator should be periodically verified—a common frequency is once a year—using National Institute of Standards and Technology (NIST)-traceable standards or NIST-accredited standards in use in other countries.

References:

- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.160(b)(4): General requirements (Laboratory Controls)
- United States Pharmacopeia (USP) General Chapter <41> Weights and Balances
- See also ASTM Standard E 617, 2013, Standard Specification for Laboratory Weights and Precision Mass Standards, West Conshohocken, PA: [ASTM International](#) (This standard is incorporated into the USP by reference; other widely recognized standards may be acceptable.)

Date: 8/4/2004

2. Is there a list of CDER-approved drug manufacturing equipment?

No. The CGMP regulations neither approve nor prohibit specific equipment for use in manufacturing of pharmaceutical products (with the exception of asbestos and fiber-releasing filters, see 21 CFR 211.72). We do not maintain a list of approved equipment. Firms are afforded the flexibility to select equipment that best satisfies their particular needs and that is capable of meeting the relevant CGMP requirements. Each firm is responsible for selecting all equipment used in their manufacturing process to produce quality products in accordance with CGMP. They are also responsible for selecting the appropriate intended use for the equipment's operation and are free to modify standard equipment designs to best suit their process and that are compatible with the product under process. The CGMPs require that equipment be of appropriate design to facilitate operations for its intended use and for cleaning and maintenance (see 21 CFR 211.63 and 211.67) and, that any equipment surface in contact with components, in-process materials, or drug products not be reactive, additive, or absorptive so as to "alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (see 21 CFR 211.65).

References:

- 21 CFR 211.63: Equipment design, size, and location
- 21 CFR 211.65: Equipment construction
- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.72: Filters

Date: 5/18/2005

3. Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness?

Yes. Since the publication of the inspection guide on cleaning validation in 1993, a number of studies have been published to demonstrate the adequacy of TOC in measuring contaminant residues.

TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation. In order for TOC to be functionally suitable, it should first be established that a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions. This is an important exercise because some organic compounds cannot be reliably detected using TOC.

TOC use may be justified for direct surface sample testing as well as indirect (rinse water) sample testing. In either case, because TOC does not identify or distinguish among different compounds containing oxidizable carbon, any detected carbon is to be attributed to the target compound(s) for comparing with the established limit. Thus, a firm should limit background carbon (i.e., carbon from sources other than the contaminant being removed) as much as possible. The established limit, or the amount of residue detected for comparison to the specification, should correct for the target material's composition of carbon. As for any cleaning method, recovery studies are necessary (21 CFR 211.160(b)). If TOC samples are being held for long periods of time before analysis, a firm should verify the impact of sample holding time on accuracy and limit of quantitation.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.160(b): General requirements (Laboratory Controls)
- USP General Chapter <643> Total Organic Carbon
- [FDA Guide to Inspections: Validation of Cleaning Processes](#)

Date: 5/18/2005

4. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through a 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?

A firm had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (nonsterile bulk powder) from a commercial source and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii* in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.

Acholeplasma laidlawii belongs to an order of *Mycoplasma*. *Mycoplasma* contain only a cell membrane and have no cell wall. They are not susceptible to beta-lactams and do not take up Gram stain. Individual organisms are pleomorphic (assume various shapes from cocci to rods to filaments), varying in size from 0.2 to 0.3 microns or smaller. It has been shown that *Acholeplasma laidlawii* is capable of penetrating a 0.2 micron filter, but is retained by a 0.1 micron filter (see Sundaram, Eisenhuth, et al. 1999). *Acholeplasma laidlawii* is known to be associated with animal-derived material, and microbiological media is often from animal sources. Environmental monitoring of *Mycoplasma* requires selective media (PPLO broth or agar).

Resolution:

For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for *Mycoplasma* and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.72: Filters
- 21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures
- Sundaram, S, J Eisenhuth, G Howard, and H Brandwein, 1999, Application of Membrane Filtration for Removal of Diminutive Bioburden Organisms in Pharmaceutical Products and Processes, *PDA J Pharm Sci Technol*, 53(4):186–201
- Kong, F, G James, S Gordon, A Zekynski, and GL Gilbert, 2001, Species-Specific PCR for Identification of Common Contaminant Mollicutes in Cell Culture, *Appl Environ Microbiol*, 67(7):3195–3200
- Murray, P, E Baron, M Pfaller, F Tenover, and R Tenover, 1995, *Manual of Clinical Microbiology*, 6th ed., Washington, DC: ASM Press

Date: 5/18/2005

5. What are the cleaning validation requirements for potent compounds (e.g., compounds that are cytotoxic, mutagenic, or have high pharmacologic activity), and is dedicated equipment required?

Separation or dedication of equipment and facilities for the manufacture of potent compounds is not specifically required by CGMP regulations. However, manufacturers should identify drugs with such risks and define the controls necessary to eliminate risk of product cross contamination in nondedicated equipment and facilities. Such controls include proper cleaning, cleaning validation, and other contaminant controls. Firms must validate that cleaning procedures are adequate to ensure that cross contamination does not occur. CGMP regulations establish requirements to guide development and execution of cleaning validation plans.

In designing a facility, firms should carefully evaluate manufacturing processes to determine the best procedural controls and floor plan—optimizing the flow of materials, equipment, and people—to help prevent product contamination.

References:

- 21 CFR 211.42: Design and construction features
- 21 CFR 211.67: Equipment cleaning and maintenance

Date: 6/8/2015

6. How do I perform cleaning validation, including for homeopathic drug products?

21 CFR 211.67(a) requires that any equipment, including dedicated and multipurpose equipment, is “cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.” You must therefore ensure that residues (e.g., active ingredients, cleaning agents) are adequately removed from product contact surfaces of all equipment during product changeovers and/or between production campaigns, depending on the types of materials and surfaces in use.

Cleaning procedures should be well-documented and consistent for their intended use. Cleaning validation programs should provide assurance that residues are effectively removed from product contact surfaces, and manufacturers should select test methods that demonstrate their effectiveness. FDA does not provide extensive guidance on conducting cleaning validation but does recommend consulting guidelines published by various trade and professional associations for additional information (e.g., International Society for Pharmaceutical Engineering, Parenteral Drug Association).

Reference:

- 21 CFR 211.67: Equipment cleaning and maintenance

Date: 6/8/2015

7. Does equipment need to be clean enough to meet limits based on the most sensitive possible methods of residue detection or quantification?

No. CGMPs require that equipment be cleaned to prevent contamination that “would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established

requirements" (see 21 CFR 211.67). The preamble to the CGMP regulations (see 43 FR 45014) indicates that this phrase was added because absolute cleanliness for multiuse equipment is neither valuable nor feasible in many circumstances. The degree of cleanliness needed, therefore, cannot depend on the method of detection because improvements in method sensitivity would necessitate ever-lower limits and ever-increasing wash cycles. Equipment should be as clean as can be reasonably achieved to a residue limit that is documented to be safe, causes no product quality concerns, and leaves no visible residues. Contamination that is reasonably avoidable and removable is never considered acceptable.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- [Preamble to the Current Good Manufacturing Practice final regulations \(43 FR 45014, Sept 29, 1978\)](#)

Date: 6/8/2015

8. Do firms need to quantify the total amount of residue remaining on equipment surfaces after manufacturing a product (before cleaning) to support cleaning validation studies?

No. In validating original cleaning procedures, firms need not quantify the level of chemical contamination remaining after manufacturing a product and before cleaning. Firms must, however, ensure that they validate proposed cleaning procedures as for routine use and should not pre-clean or otherwise attempt to make it easier for the procedures being validated to meet their cleaning objectives.

For example, batches significantly smaller than full-scale would not offer sufficient assurance that the cleaning procedure could reliably remove residues to acceptable levels after full-scale production. The material being cleaned should be manufactured at a similar scale and manner as during validation. Also, firms should sample equipment that is stored uncleaned for a longer time than validated to demonstrate that their cleaning procedures are effective.

Once equipment surfaces are cleaned by validated procedures, firms generally are not expected to analytically examine them after each cleaning. (Manual cleaning methods may be an exception to this general rule because of inherent variability in operator compliance and abilities.) However, a residue-monitoring program whose frequency and methods have been determined by risk assessment is recommended.

Reference:

- [FDA Guide to Inspections: Validation of Cleaning Processes](#)

Date: 6/8/2015

9. Should laboratory glassware be included in a firm's equipment cleaning validation program?

No. FDA does not expect laboratory glassware to be included in the processing equipment cleaning validation program. Glassware must, of course, be clean, and CGMP regulations consider laboratory equipment to be included within the scope of 21 CFR 211.67. Cleanliness is best assessed by inspecting laboratory procedures for the following:

- Use of nondedicated glassware and other equipment
- Method validation (e.g., ruggedness)
- Absence of extraneous or interfering data in the results of sample analyses

Laboratory cleaning procedures may include repetitive rinses with the solvent used to prepare the analyte, followed by oven drying. The equipment need not be swabbed or otherwise tested to ensure removal of potentially contaminating residues. A firm may elect to sample its glassware for residual contamination to exclude or explore the possibility of interference in the case of particularly sensitive analyses or difficult-to-clean compounds.

The possibility of carryover contamination affecting a method's performance or integrity of the results is generally considered of low risk to the product and consumers, with the exception of potent compounds. Contaminated laboratory equipment, however, should not be a frequent excuse for rejecting or discarding aberrant results. Glassware that is not properly cleaned can make it difficult to determine if the source of aberrant analytical results is related to the unclean glassware or residues from manufacturing equipment. We expect firms to maintain laboratory equipment in a clean and sanitary manner to provide confidence in the analytical results.

Reference:

- 21 CFR 211.67: Equipment cleaning and maintenance

Date: 6/8/2015

10. What is an acceptable level of detergent residue, and what is the basis for arriving at this level, if any?

It is the firm's responsibility to establish acceptance limits and to be prepared to provide the basis for those limits to FDA. Thus, there is no universal standard for levels of detergent residue. Residues must not exceed their established acceptance limits and must not adversely alter drug product safety, efficacy, quality, or stability (see references below).

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- [FDA Guide to Inspections:Validation of Cleaning Processes](#)

Date: 6/8/2015

11. If a procedure's ability to clean a piece of equipment made of a particular material, such as 316 stainless steel, is acceptable and validated, can that "material-specific" cleaning procedure be applied to other pieces of equipment and compounds without extensive validation?

No. In establishing an effective cleaning procedure for a particular piece of equipment, firms must consider its material of construction/fabrication, exact design, conditions of use, and, in particular, the specific substances that could contaminate the equipment. Therefore, to demonstrate proof of cleaning for a given piece of equipment, firms should have data that relate to all of these factors.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- [FDA Guide to Inspections:Validation of Cleaning Processes](#)

Date: 6/8/2015

12. Is testing rinse solution enough to support residue determinations for cleaning validation?

No. For cleaning validation, rinse samples alone would not be acceptable; firms should also measure the residue or contaminant on the equipment surface using a direct method (if feasible). One disadvantage of rinse samples is that the rinse solvent may not remove the residue or contaminant.

Rinse samples are capable of sampling large surface areas, particularly ones that are difficult to access; therefore, some firms use both swab and rinse samples during the course of their cleaning validation. This is acceptable if the rinse solvent has been demonstrated to dissolve residues of concern and is otherwise suitable for use on the surfaces to be sampled.

For routine equipment cleaning after validation, a residue-monitoring program whose frequency and methods have been determined by risk assessment is recommended to demonstrate that the validated process continues to consistently clean the equipment.

The purpose of cleaning validation is to demonstrate that a particular cleaning process will consistently clean the equipment to a predetermined standard; the sampling and analytical test methods should be scientifically sound and should provide adequate scientific rationale to support the validation.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- [FDA Guide to Inspections:Validation of Cleaning Processes](#)

Date: 6/8/2015

13. Does FDA prefer one type of material over another (e.g., polyvinylidene difluoride over stainless steel) for construction of recirculating loops in water for injection (WFI) systems?

No. There is no official agency preference for one material over another. Whatever material a firm selects for its WFI system must be suitable for its intended use. This holds true for virtually all production equipment.

When evaluating the suitability of a WFI system's piping, consider the surface texture or finish of the piping's interior wall (e.g., smoothness, waviness), its ability to resist high temperatures and pressures, and its ability to withstand sterilizing and sanitizing agents and procedures.

Equipment surfaces that are in contact with components, in-process materials, or drug products must not be reactive, additive, or absorptive so as to alter the drug product's safety, identity, strength, quality, or purity beyond its official or established requirements.

References:

- 21 CFR 211.65: Equipment construction
- 21 CFR 211.67: Equipment cleaning and maintenance

Date: 6/8/2015

Contact for further information:

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4.4. Control of Components and Drug Product Containers and Closures

1. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?

The CGMP regulations (21 CFR parts 210 and 211) for finished pharmaceutical manufacturing do not specifically address the requirement to conduct, or to keep records of, internal quality assurance audits. If the report in question was from a routine audit to verify that the firm's quality system is operating as intended, then it would be acceptable if the firm elected to discard the report once all corrections have been verified.

However, any documentation of corrective action as a result of such an audit would have to be retained (see §§ 211.180 and 211.188). For example, if a routine internal audit finds a problem with a mixing step and the outcome is a change in mixing time, all affected procedures, including the master production record, are to reflect the necessary changes, and such records are subject to FDA inspection as usual. Any investigation into the impact this problem had on related batches is to be retained and also made available for inspection by FDA (see § 211.192).

In addition, any reports of investigations or evaluations prepared in response to, for example, a product complaint (§ 211.198), vendor qualification (§ 211.84), periodic review of records and data (§ 211.180(e)), and a failure investigation (§ 211.192) are not internal audits as discussed above. Such records are subject to FDA inspection and must be retained for at least the time specified in the CGMP regulations (see § 211.180).

References:

- 21 CFR 211.84: Testing and approval/rejection of components, drug product containers, and closures
- 21 CFR 211.180: General requirements
- 21 CFR 211.188: Batch production and control records
- 21 CFR 211.192: Production record review
- 21 CFR 211.198: Complaint files
- [Preamble to the Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding](#) regulations (43 FR 45015, paragraph 4, Sept 29, 1978)
- Compliance Policy Guide Sec. 130.300 [FDA Access to Results of Quality Assurance Program Audits and Inspections](#) (CPG 7151.02)

2. Can containers, closures, and packaging materials be sampled for receipt examination in the warehouse?

Yes. Generally, we believe that sampling in a typical drug manufacturing facility warehouse would not represent a risk to the container or closure or affect the integrity of the sample results. But whether the act of collecting a sample in the warehouse violates the CGMP requirement that containers "be opened, sampled, and sealed in a manner designed to prevent contamination of their contents..." will

depend on the purported quality characteristics of the material under sample and the warehouse environment. For containers or closures purporting to be sterile or depyrogenated, sampling should be under conditions equivalent to the purported quality of the material: a warehouse environment would not suffice (see 21 CFR 211.94 and 211.113(b)). This is to preserve the fitness for use of the remaining containers or closures as well as to ensure sample integrity, if they are to be examined for microbial contamination. At a minimum, any sampling should be performed in a manner to limit exposure to the environment during and after the time samples are removed (i.e., wiping outside surfaces, limiting time that the original package is open, and properly resealing the original package). Well-written and followed procedures are the critical elements.

Note that the CGMPs at 21 CFR 211.84 permit a manufacturer to release for use a shipment of containers or closures based on the supplier's certificate of analysis and a visual identification of the containers or closures. Once a supplier's reliability has been established by validation of their test results, a manufacturer could perform the visual examination entirely in the warehouse.

References:

- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures
- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 211.113(b): Control of microbiological contamination
- 21 CFR 211.122: Materials examination and usage criteria

3. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through a 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?

A firm had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (nonsterile bulk powder) from a commercial source and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii* in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.

Acholeplasma laidlawii belongs to an order of *Mycoplasma*. *Mycoplasma* contain only a cell membrane and have no cell wall. They are not susceptible to beta-lactams and do not take up Gram stain. Individual organisms are pleomorphic (assume various shapes from cocci to rods to filaments), varying in size from 0.2 to 0.3 microns or smaller. It has been shown that *Acholeplasma laidlawii* is capable of penetrating a 0.2 micron filter, but is retained by a 0.1 micron filter (see Sundaram, Eisenhuth, et al. 1999). *Acholeplasma laidlawii* is known to be associated with animal-derived material, and microbiological media is often from animal sources. Environmental monitoring of *Mycoplasma* requires selective media (PPLO broth or agar).

Resolution:

For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for *Mycoplasma* and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.72: Filters
- 21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures

- Sundaram, S, J Eisenhuth, G Howard, and H Brandwein, 1999, Application of Membrane Filtration for Removal of Diminutive Bioburden Organisms in Pharmaceutical Products and Processes, *PDA J Pharm Sci Technol*, 53(4):186–201
- Kong, F, G James, S Gordon, A Zekynski, and GL Gilbert, 2001, Species-Specific PCR for Identification of Common Contaminant Mollicutes in Cell Culture, *Appl Environ Microbiol*, 67(7):3195–3200
- Murray, P, E Baron, M Pfaller, F Tenover, and R Tenover, 1995, *Manual of Clinical Microbiology*, 6th ed., Washington, DC: ASM Press

Date: 5/18/2005

4. How many containers of each component from each shipment must a firm sample and test to comply with the CGMP requirements for identity testing? Do the CGMPs permit the identity test on a pooled, or composite, sample of multiple containers?

The CGMP regulations address component sampling and testing primarily at 21 CFR 211.84. These regulations require representative samples of each shipment of each lot of active and inactive component (or raw materials) to be tested to confirm the identity of the component as labeled prior to release for use in drug product manufacturing. The regulations acknowledge that more than one test may be needed to ascertain a component's identity. For the purpose of this answer, a component's identity is its chemical structure and its physical form (e.g., polymorph, solvate, and appearance) including, if appropriate, its stereochemistry or immunochemistry. (See also ICH guidances for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*.)

The CGMP regulations do not specify the number of containers to be sampled from each received shipment. However, § 211.84(b) establishes the principles to be followed in designing a sampling program for components. The requirements of this section can be summarized as follows:

- Samples are to be representative of the shipment received.
- The number of containers sampled as well as the amount of material sampled from each container is to be based on statistical criteria for component variability, confidence levels, and the degree of precision required.
- The sample program takes into account the past quality history of the supplier.
- The sample amount is to be sufficient for the necessary analysis and reserve samples.

The first three are most relevant to the question of how many containers to sample for identity testing, i.e., representative sampling, tolerance for variability and confidence required, and past history. (The amount needed for analysis and reserve can be readily met by sampling even one container, so the number of containers is not an important issue once the shipment's identity is verified.)

Unlike most component attributes, a component's identity is generally a discrete variable, i.e., the material in the container either is or is not what the label purports it to be. The component container's content might differ from what the container label states due to mistakes in filling and labeling by the supplier or repacker, or as a result of the substitution of a container's contents during distribution and warehousing before receipt by the drug product manufacturer. Using a wrong component in processing could result in a serious public health hazard. For these reasons, manufacturers need to develop an approach that provides a high degree of confidence that each container in each shipment contains the material purported by the label. (See also 21 CFR 211.160(b), which requires all sampling to be representative and scientifically sound.) The approach must account for the fact that the material's identity must not vary from what is specified. The past quality history of a supplier and the scope of their operations is relevant to the chance for mistakes to occur under a supplier's control, but does not necessarily bear on what happens to a drug once it is outside the supplier's control.

How many containers of each component from each shipment must a firm sample and test to comply with the CGMP requirements for identity testing?

The regulation at § 211.84 requires that representative samples of each shipment of each lot shall be collected for testing. Some manufacturers have interpreted the CGMPs to require that each container in a shipment be sampled and tested for the attribute of identity. Testing samples from every container to determine identity may be valuable particularly for components purchased from distributors. (Analytical equipment and methods are readily available that permit rapid, nondestructive identification of material directly in containers in a warehouse area.) The CGMPs permit each drug product manufacturer to make its own decision as to the number of containers to sample, as long as

the sampling plan is scientifically sound, leads to representative samples, and complies with the principles established at § 211.84(b). An important caveat applies with respect to § 211.84: samples are to be taken by the drug product manufacturer from containers after receipt (i.e., pre-shipment samples or so-called *piggyback* samples are generally not acceptable).

Do the CGMPs permit the identity test on a pooled, or composite, sample of multiple containers?

The CGMPs address the issue of sample compositing directly but only in the context of individual container sampling. Section 211.84(c)(4) explicitly prohibits compositing samples taken from the top, middle, and bottom of a single container when such stratified sampling is considered necessary (as might be the case when moisture content needs to be controlled, particularly when only a portion of a container may be used in a drug product batch). The preamble for § 211.84(c)(4) explains further that there "is no general prohibition... on compositing samples [from single containers] where such compositing would not mask subdivisions of the sample that do not meet specifications" (see [1978 preamble](#), paragraph 231).

Testing individual samples from multiple containers provides a high level of assurance and is consistent with CGMP. Testing a composite sample for identity could satisfy the CGMP regulations (§§ 211.84 and 211.160) but only if a manufacturer demonstrates either that the detection of a single nonconforming container is not masked by compositing or that an additional test(s) routinely performed on the composite sample ensures that all containers sampled contain the same material. Thus, a purity assay on a composite sample prepared by mixing equal aliquots from each container may be acceptable provided such a test is sufficiently sensitive to reveal the presence of a single nonconforming container.

References:

- Preamble to the Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding regulations (43 FR 45014, Sept 29, 1978)
- [21 CFR 211.82](#): Receipt and storage of untested components, drug product containers, and closures
- [21 CFR 211.84](#): Testing and approval or rejection of components, drug product containers, and closures
- [21 CFR 211.160](#): General requirements (Laboratory Controls)
- FDA Guidance for Industry, 2000, ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances [[Text](#) or [PDF](#)]
- FDA Guidance for Industry, 1999, ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products [[PDF](#)]

5. What methods of analysis are suitable for testing for melamine contamination in pharmaceutical components?

FDA recommends using a method demonstrated to be suitable for detecting melamine adulteration based on the manufacturer's risk assessment and prevention strategy. The manufacturer's selection of a sampling approach and test method sensitivity should address the possibility that (1) melamine might not be uniformly distributed in an at-risk component, or (2) that the source of intentional melamine contamination might be the starting material used to produce the at-risk component. The guidance for industry *Pharmaceutical Components at Risk for Melamine Contamination* provides a link to assay methods capable of detecting melamine at levels as low as 2.5ppm. These methods can detect melamine and cyanuric acid in complex matrices (protein materials) and, therefore, may be useful in developing test methods for other at-risk drug components. FDA also recognizes that a less sensitive method might also be appropriate for screening in certain cases.

References:

- 21 CFR part 211, subpart E: Control of Components and Drug Product Containers and Closures
- FDA Guidance for Industry, 2009, [Pharmaceutical Components at Risk for Melamine Contamination](#)

Date: 12/17/2009

6. Does FDA require or recommend any special precautions or controls over the manufacturing of animal-derived drug ingredients to prevent contamination?

Yes, FDA requires that animal-derived ingredients be controlled in a manner to ensure that contamination does not occur, beginning with initial collection and handling of the animal-derived material through its processing and subsequent use in a finished pharmaceutical. See, for example, the Federal Food, Drug, and Cosmetic Act (FD&C Act) sections 501(a)(2)(A) and 501(a)(2)(B). FDA has special concerns regarding the vulnerability of animal-derived ingredients to contamination by pathogenic agents (i.e., agents that can cause disease or illness in humans or other animals). As background, ingredients are also called *components*, and there are two categories of components used in finished pharmaceutical production: inactive ingredient (often called *excipients*) and active ingredient (often called *active pharmaceutical ingredient (API)*). For the purpose of this guidance, an animal-derived ingredient is a substance of animal origin used to manufacture a drug product. They are primarily derived from byproducts of food production and include extractions from certain animal material and milked animal fluids (e.g., venoms) and may even be human-derived. Products of animal cell cultures, including monoclonal antibodies and therapeutic proteins, are not considered animal-derived APIs for the purpose of this guidance. For additional information concerning biotechnology products, refer to ICH guidance for industry *Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*. Ingredient manufacturers are responsible for the quality and safety of the material they produce for use in finished pharmaceuticals. Ingredients are drugs and drugs are required to conform with current good manufacturing practice (FD&C Act, section 501(a)(2)(B)). Finished pharmaceutical manufacturers are also responsible for their selection, qualification, and use of ingredients in finished pharmaceuticals (e.g., the CGMP regulations at 21 CFR part 211, subpart E). Ingredient and finished pharmaceutical manufacturers should fully understand the potential for pathogenic agent contamination beginning with the livestock processing establishment (LPE) and continuing through subsequent handling and processing, and establish stringent controls to prevent contamination. It is also essential that appropriate tests or examinations are developed and applied to detect contamination as part of any meaningful control program.

References:

- FD&C Act, sections 501(a)(2)(A) and 501(a)(2)(B)
- 21 CFR part 211, subpart E: Control of Components and Drug Product Containers and Closures
- FDA Guidance for Industry, 1998, ICH Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

Date: 1/27/2011

7. What are FDA's primary concerns about pathogenic agent contamination of animal-derived drug ingredients?

FDA is concerned about contamination of animal-derived ingredients by pathogenic agents during processing at the LPE, at a subsequent consolidator of animal material or raw material processing plant, or during the manufacturing process to create the final ingredient. One should assume that animal-derived materials will not only harbor but will often support growth of pathogens and accordingly should ensure appropriate control over the handling and processing of these materials. Current good manufacturing practice is to be followed in handling such material to ensure that contamination does not occur that would affect the material's quality and purity, or that would be harmful when the product is administered to patients. Pathogenic agent contamination includes bacteria, molds, viruses, protozoa, parasites, and prions. Pathogenic agents can enter the manufacturing facility within the animal material and contaminate excipients, water, processing equipment, personnel, environment, or packaging. Contaminated drug ingredients present potential health risks that may affect various patient populations, including immune-compromised patients, as well as otherwise healthy people of all ages. An agent may be considered pathogenic if its presence represents a significant risk to patient safety. Factors affecting the pathogenic agent's ability to cause harm include the:

- Nature of the agent (pathogenicity, virulence)
- Amount of the pathogenic agent
- Type of manufacturing process and whether it affects the pathogenic agent's ability to survive
- Ability of the pathogenic agent to grow within the ingredient
- Type of drug product, and its route and length of administration
- Patient population for the drug product (including the most vulnerable patients who may take the drug).

Date: 1/27/2011

8. What manufacturing contamination risks are presented by the different pathogenic agents?

Manufacturing contamination risks presented by the different pathogenic agents can include the following:

Vegetative Bacteria Vegetative bacteria are actively growing and reproducing bacteria. If there are no steps in the manufacturing process to kill vegetative bacteria, they can proliferate and accumulate during drug ingredient processing.

Toxin-Producing Microorganisms Several genera and species of microorganisms are capable of producing toxins. Microbial toxins can be divided into two general groups: exotoxins and endotoxins. An exotoxin is a soluble protein excreted by a microorganism, including bacteria, fungi, algae, and protozoa. Exotoxins can include heat-stable toxins that remain active at temperatures as high as 100°C or heat-labile toxins that are readily inactivated by heat treatment. Exotoxins, especially heat-stable exotoxins, can remain in the ingredient throughout the manufacturing process and adversely affect patient health. An endotoxin is a component of the outer membrane of a Gram-negative bacterium. Unlike exotoxins, endotoxins are only released when the organisms are disrupted or destroyed. Endotoxins are heat- and chemical-resistant and, if injected, may induce reactions including febrile effect, hypotension, and shock.

Spore-Forming Bacteria Spore-forming bacteria can be difficult to eliminate from the manufacturing environment because the spores may be extremely resistant to heat, freezing, extreme pH, desiccation, and chemicals. Spore-forming bacteria can produce exotoxins and can remain dormant without nutrients for extended periods. Spores can be resistant to harsh manufacturing processes that will kill vegetative bacteria. When dormant spores are reintroduced into an acceptable germination environment they can become active reproductive vegetative cells. Once spores germinate and begin reproducing as vegetative cells, production of exotoxins can occur in a short period of time.

Fungi/Molds Molds are a subset of fungi that reproduce by releasing spores into the air which, if they land on a moist nutrient source or animal tissue, can germinate. Some species of molds produce toxic byproducts called *mycotoxins*. Mycotoxins can accumulate in animal tissues, rendering the affected organs/tissues unfit for use as a source of starting material for the production of animal-derived drug ingredients. It is important to prevent molds from growing in drug ingredients and when feasible and valuable remove all molds that may contaminate such ingredients. Yeasts, another type of fungi, can also be pathogenic or cause spoilage of an ingredient.

Viruses Although a virus can only multiply within its host, the inadvertent use of material from virus-infected animals or contact of the drug ingredient with virus-contaminated surfaces can transmit viral particles to patients. Virus survival rates differ based on virus type and variables associated with surface materials that become contaminated. On hard, nonporous surfaces, some virus species can survive and remain transmissible for days or weeks. The probability of an animal virus contaminating an animal-derived ingredient will depend on the viral load of the raw material (e.g., tissue, glands, blood) and the viral clearance capability of the drug ingredient manufacturing process. Both of these factors should be considered when assessing the risk of viral contamination of the ingredient.

Internal Animal Parasites Transmission of internal parasites occurs from host to host through consumption of contaminated food or water. Parasites live and reproduce within the tissues and organs of infected hosts and are often excreted in feces. Government inspectors are trained to look for internal parasites and prevent unhealthy animals from entering the food supply. Animals deemed fit for food consumption are inspected and certified as healthy.

Prions Protection from prion contamination includes obtaining bovine meat and meat byproducts from animals not infected with bovine spongiform encephalopathy and protecting against contamination of product with high-risk tissues, especially brain and spinal cord tissue. Drug manufacturers importing bovine material into the United States should be familiar with and adhere to all import eligibility requirements and government regulations pertaining to food and drugs. It is important that farms, slaughterhouses, and renderers observe government regulations prohibiting the use of unhealthy animals in the food supply. Animals deemed fit for food consumption are normally inspected and certified as healthy in many countries.

Date: 1/27/2011

9. What are some ways to minimize pathogenic agent contamination in incoming animal-derived raw material?

The drug component and finished product CGMP guidances and regulations emphasize prevention of problems and avoidance of contamination rather than final testing or examination alone. In other words, control strategies that prevent contamination are central to CGMP, while control strategies based on testing alone do not comply with CGMPs. Raw materials from animals can have microbial

pathogen health risks based on country of origin, LPE processing, transportation, and manufacturing processing. Under the right circumstances, raw material from animals can provide a suitable (e.g., nutrient-rich) environment for bacteria and mold to proliferate, or for viruses and other pathogenic agents to remain infective. If undetected contaminated raw material enters the manufacturing process, it can remain pathogenic in the product and a hazard to the consumer. The manufacturing conditions used in most ingredient manufacturing processes are often insufficient to eliminate all pathogenic agents from the ingredient. Methods of minimizing contamination of raw material with pathogenic agents may include the following:

- Animal source

When animal-derived material is used, it is important that it be derived from healthy, disease-free animals. The occurrence of pathogens can vary greatly among different animal species. Ingredient manufacturers should understand the pathogenic risks associated with different animal species and with different organs, glands, or tissues within species. Drug ingredient manufacturers should be aware that even healthy animals can be reservoirs for pathogenic agents and improper handling can spread contamination. If improperly handled, microbial contamination can transfer to uncontaminated tissues and cause contamination.

Ensuring the health of U.S. livestock is the responsibility of many Federal agencies, most of which are part of the U.S. Department of Agriculture (USDA). Animal-health and food-safety regulations are detailed in titles 9 and 21 of the Code of Federal Regulations. Animal health authorities in each State develop regulations that are consistent with the Federal agencies and are responsible for monitoring and controlling diseases in the State's domestic livestock and poultry. State inspectors ensure compliance by companies with individual State standards as well as with Federal meat and poultry inspection statutes. States assist in controlling diseases through inspections, testing, vaccinations, treatments, quarantines, and other activities.

Awareness of the conditions of control and monitoring of source animals will aid in determining which animals and animal parts are appropriate for drug product manufacturing.

- LPE

Ingredient manufacturers should consider auditing the LPEs supplying raw materials to them and ensure their compliance with all Federal and State government regulations. It is recommended that manufacturers develop standard operating procedures and define sanitation requirements of raw materials immediately after butchering, including, for example, the following:

- Chilling requirements, if indicated, including temperature ranges and how soon after butchering chilling should begin
- Chemical preservation methods, if indicated, including types and concentrations of chemical preservatives used
- Storage processes, including sanitization of containers and container type/material (e.g., stainless steel vs. food grade plastics)
- Transportation criteria, including sanitization of containers, if different from storage and temperature ranges

The overall contamination of carcasses with pathogens depends on not only the prevalence and numbers of the pathogens on the hair, skin, and in the intestinal tract of the animal, but is significantly affected by the degree of cross contamination occurring from these sources during slaughter and processing (see USDA references, below, for additional information). FDA expects that manufacturers will establish appropriate specifications for bioburden in their in-coming raw materials.

References:

- [USDA Animal and Plant Health Inspection Service](#)
- [USDA Animal and Plant Health Inspection Service, Import and Export](#)
- [USDA Food Safety and Inspection Service, Parasites and Foodborne Illness Fact Sheet](#)

Date: 1/27/2011

10. Are there control measures for minimizing pathogenic agent contamination in animal-derived drug ingredient manufacturing facilities?

Yes, control measures may include the following:

- Process control

Holding and processing times for animal-derived material should be minimized to reduce the likelihood of microbial proliferation. The process qualification studies should include microbial sampling at multiple time points to evaluate the effects of time, temperature, and processing conditions on microbial growth. Routine microbial identification will provide valuable information regarding the types of organisms present in incoming material and throughout the manufacturing process. Processing conditions can then be adjusted to help control the number and types of organisms present during the manufacturing process. Spores and many bacteria can be removed by filtration when filtration or filtration cascade systems are possible. Usually filters with a pore size rating of 0.45 micron or smaller will remove spores and many bacteria from a preparation. Viruses and many toxins are heat labile so a heat treatment should be considered early in process development. Many purification and concentration systems may have antimicrobial effects. The timing and sequence location in the process along with appropriate holding and processing times may serve to optimize the antimicrobial effects of the processes.

Development of process monitoring tests and acceptance criteria should be established during the process development stage.

- Facility and equipment controls

Facilities can also be reservoirs for pathogenic agents. Maintaining a facility within CGMP should include but not be limited to:

- Having adequately trained staff
- Using suitable quality water during manufacturing
- Having a facility design that minimizes the risk of cross contamination
- Providing for proper storage of the ingredient

Cleaning procedures should include cleaning of facilities and equipment that ensures the removal of all raw materials between batches. Designing an effective cleaning program involves setting specific standards, understanding the facility's microbial environmental isolates, and selecting the right disinfecting agents to inactivate isolates that may be in the product or in the environment. Ingredient manufacturers should use sporicidal agents at appropriate intervals in the cleaning schedule to destroy bacterial and fungal spores.

References:

- FDA Guidance for Industry, 2001, [ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients](#)
- United States Pharmacopeia (USP) General Information Chapter <1072> Disinfectants and Antiseptics (USP33–NF 28 Reissue, 2010)
- Wiley, JM, L Sherwood, and CJ Woolverton, 2008, Prescott, Harley and Klein's Microbiology, Boston: McGraw-Hill Higher Education.

11. What should drug manufacturers do to prevent formation of glass lamellae (glass fragments) in injectable drugs filled in small-volume glass vials?

Under certain conditions, glass vials can shed thin, flexible fragments called *glass lamellae* (Lachman, Lieberman, et al. 1986; Iacocca, Toltl, et al. 2010). These lamellae are shed from the interior surface of the glass container directly into the drug and are difficult to detect by visual inspection. Several drugs have been recalled due to this problem: epoetin alfa, methotrexate, hyaluronidase recombinant, and fluorouracil (see [Enforcement Reports](#) on FDA's Web Site). No adverse events to date have been reported nor can be directly attributed to this phenomenon. However, there is the potential for drugs administered intravenously that contain these fragments to cause embolic, thrombotic, and other vascular events (e.g., phlebitis); and, when administered subcutaneously, to lead to development of foreign body granuloma, local injection site reactions, and increased immunogenicity (Singh, Afonina, et al. 2010). The following conditions have been associated with a higher incidence of the formation of glass lamellae:

- Glass vials manufactured by a tubing process (and thus manufactured under higher heat). These vials are less resistant than molded glass vials and may shed lamellae more easily (Ennis, Pritchard, et al. 2001). The processing conditions used to manufacture glass vials can be designed to mitigate the potential for later delamination.
- Drug solutions formulated at high pH (alkaline) and with certain buffers. Common buffers associated with lamellae formation include citrate and tartrate (Sacha, et al. 2010).

- Length of time the drug product is exposed to the inner surface of the container. The time duration has a direct correlation to the potential for glass lamellae formation to occur during the product shelf life (Lachman, Lieberman, et al. 1986).
- Drug products with room temperature storage requirements. Drugs stored at room temperature have a greater chance of glass lamellae formation than do products stored at colder temperatures (Iacocca and Allgeier 2007).
- Terminal sterilization has a significant effect on glass stability (Iacocca, Tolti, et al. 2010).

The referenced literature, below, includes recommended actions to help prevent the formation of glass lamellae. For example, for products "at risk," the vial surface alkalinity can be minimized by proper selection of glass composition (e.g., highly resistant, nonalkaline earth borosilicate glass), appropriate selection and qualification of vendors, and proper quality control of the incoming vials. Accordingly, FDA advises drug manufacturers of products to reexamine their supplier quality management program with the glass vial manufacturers to ensure that this phenomenon is not occurring. Further, the Agency reminds finished drug product manufacturers that CGMP regulations require that drug containers not be reactive or additive so as to alter the safety or quality of the drug. See 21 CFR 211.94; [Rx-360's Web site](#), which has commented on the issue of delamination; and deviation reporting regulations for field alert reports (21 CFR 314.81) and biological product deviation reports (21 CFR 600.14).

References:

- Lachman, L, H Lieberman, and J Kanig, 1986, The Theory and Practice of Industrial Pharmacy, 3rd ed., Philadelphia: Lippincott Williams & Wilkins, 645–649, 796–798
- Iacocca, RG, N Tolti, et al., 2010, Factors Affecting the Chemical Durability of Glass Used in the Pharmaceutical Industry, AAPS Pharm Sci Tech, DOI:10.1208/s12249-010-9506-9
- Singh SK, N Afonina, et al., 2010, An Industry Perspective on the Monitoring of Subvisible Particles as a Quality Attribute for Protein Therapeutics, J Pharm Sci, 99(8):3302–3321
- Ennis RD, R Pritchard, et al., 2001, Glass Vials for Small Volume Parenterals: Influence of Drug and Manufacturing Process on Glass Delamination, Pharm Dev and Tech, 6(3):393–405
- Sacha, G., et al., 2010, Practical Fundamentals of Glass, Rubber, and Plastic Sterile Packaging Systems, Pharm Dev and Tech, 15(1):6–34
- Iacocca, RG, and M Allgeier, 2007, Corrosive Attack of Glass by a Pharmaceutical Compound, J Mater Sci, 42:801–811
- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 314.81: Other postmarketing reports
- 21 CFR 600.14: Reporting of biological product deviations by licensed manufacturers

Date: 3/25/2011

12. Are there any special processing or handling concerns for flexible intravenous (IV) solution bags?

Yes, due to their soft and flexible design, IV solution bags can be easily damaged if not handled properly during processing and labeling. A damaged IV solution bag may not protect the contents from exposure to microbiological contamination as intended. Detection of a damaged IV solution bag by leaks or by examination of the bag may not be possible. In fact, a microscopic defect may not be evident until microbiological contamination becomes visible, which is too late. Prevention of this potentially serious problem is important. FDA is aware of product recalls where IV products in flexible plastic bags were exposed to rough surfaces or sharp objects during labeling, creating microscopic punctures or weakening the bag surfaces. When a compromised IV solution bag is filled with liquid and expands as intended, holes may form at the weak points, leading to a loss of sterility or assurance of sterility.

Manufacturers are reminded that drug product containers and closures must be handled and stored in a manner to prevent contamination (see 21 CFR 211.80(b) and also 211.94).

References:

- 21 CFR 211.80(b): General requirements
- 21 CFR 211.94: Drug product containers and closures

Date: 7/5/2011

13. What can IV drug manufactures do to help prevent the loss of sterility due to compromised IV solution bag integrity during labeling?

The risk of loss of sterility during labeling can be reduced through the use of nonimpression printing devices for labeling. If a manufacturer uses labeling equipment to apply a label on an IV solution bag and that labeling equipment makes an impression on the IV bag, procedures should be in place to inspect the labeling equipment regularly, particularly after any maintenance is performed. Manufacturing equipment must not have any rough or sharp surfaces that will create punctures or areas of weakness in the IV solution bags. Prevention is important: damaged IV bags may elude detection by standard examinations and tests, including checks for leaks. Manufacturers are reminded that equipment maintenance and cleaning must be appropriate to prevent malfunctions or contamination that would alter the quality or purity of a drug product (see 21 CFR 211.67).

Additional information: FDA Guidances

- [Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice](#)
- [Container Closure Systems for Packaging Human Drugs and Biologics](#)

References:

- 21 CFR part 211: [Current Good Manufacturing Practice for Finished Pharmaceuticals](#)
- 21 CFR 211.22: Responsibilities of quality control unit
- 21 CFR 211.80: General requirements (for the control of components and containers)
- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.100: Written procedures; deviations

[Recall announcements](#) [FDA Warning Letters](#) Date: 7/5/2011

14. Must each batch of a United States Pharmacopeia (USP)-grade API be tested using the analytical procedures specified in the USP monograph?

No; however, in the event of a dispute, the compendial method is considered conclusive (see USP reference, below). Section 201(g) of the FD&C Act includes “articles intended for use as a component” of a finished drug product, including APIs (or drug substances), under its definition of a *drug*, and section 501(b) requires a drug recognized in USP to meet the standards of strength, quality, and purity in the official monograph or to be clearly labeled to designate how it differs from USP standards. Although each batch of a compendial article must conform to the monograph specifications/acceptance criteria, the analytical procedures used to show conformance may differ from official USP methods **if** the alternative methods are fully validated, suitable for use, and give equivalent or better results than the official USP method. All APIs must also be manufactured in compliance with CGMP as stated in section 501(a)(2)(B) of the FD&C Act.

References:

- [FD&C Act Chapter V: Drugs and Devices](#)
- USP 38–National Formulary (NF) 33 (2015) General Notices, Section 6.30

Date: 6/9/2015

15. Who is responsible for analytically testing APIs to ensure they comply with their specifications and with USP requirements, if any? API manufacturers perform analytical testing on APIs to confirm that they meet all applicable specifications established for release. Finished drug product manufacturers ensure that APIs used in their products meet all of their established specifications and—for compendial APIs—meet USP requirements. Additional information is provided below.

API Manufacturer Responsibilities Section 501(a)(2)(B) of the FD&C Act requires all drugs (including APIs) to be manufactured in compliance with CGMP. FDA therefore expects API manufacturers to follow the recommendations in ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. API labeling supplied by the API manufacturer includes a certificate of analysis (COA). Section 11.4 of ICH Q7 recommends that the API manufacturer’s COA should include, as applicable, the API’s name, grade, batch/lot number, date

of release, and a list of “each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained” For example, for a compendial-grade API, the COA should identify the compendial tests that were performed (as well as customer-specified tests, if any) and the test results. If a compendial-grade API differs from a USP standard of strength, quality, or purity, that difference should be clearly declared on the label.

Finished Drug Product Manufacturer Responsibilities In the CGMP regulations for finished pharmaceuticals, 21 CFR 211.80 states that “[T]here shall be written procedures describing in sufficient detail the . . . testing . . . of [finished drug product] components” Additionally, 21 CFR 211.84(d)(2) states that “[E]ach component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier’s analyses through appropriate validation of the supplier’s test results at appropriate intervals.” Therefore, if the finished drug product manufacturer accepts the test results from an API supplier’s COA rather than performing the tests itself (other than for identity, which the manufacturer is required to perform), the manufacturer must validate the API supplier’s reliability. This validation procedure is established by the finished drug product manufacturer and should be consistent with the principles of CGMP and risk management. The finished drug product manufacturer should also ensure that compendial-grade APIs comply with compendial specifications, either by testing the APIs or by validating API suppliers’ reliability, as described above.

References:

- [FD&C Act Chapter V: Drugs and Devices](#)
- 21 CFR 211.80: General requirements
- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers and closures
- FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Date: 6/9/2015

Contact for further information: CDER-OPQ-Inquiries@fda.hhs.gov

4.5. Production and Process Controls

1. Do the CGMPs require a firm to retain the equipment status identification labels with the batch record or other file? Assuming each major piece of equipment has a unique cleaning and use log that is adequately retained, is it acceptable to discard these *quick reference* equipment labels?

The CGMP regulations for finished pharmaceuticals require the retention of cleaning and use logs for non-dedicated equipment, but no similar requirement exists for retaining what are intended to be *quick reference* or temporary status labels. Examples of these kinds of status labels include *mixing lot ###; clean, ready for use as of d/m/y;* and *not clean*. We see no value in the retention of such labels in addition to the required equipment log or batch record documentation. The labels serve a valuable, temporary purpose of positively identifying the current status of equipment and the material under process. Any status label should be correct, legible, readily visible, and associated with the correct piece of equipment. The information on the temporary status label should correspond with the information recorded in the equipment cleaning and use log, or the previous batch record for nondedicated equipment.

Labels are merely one way to display temporary status information about a piece of equipment. It is considered acceptable practice to display temporary equipment status information on dry-erase boards or chalkboards. And it would be appropriate for an FDA investigator to verify that the information on a temporary status label is consistent with the log.

References:

- 21 CFR 211.182: Equipment cleaning and use log
- 21 CFR 211.105: Equipment identification

2. Can containers, closures, and packaging materials be sampled for receipt examination in the warehouse?

Yes. Generally, we believe that sampling in a typical drug manufacturing facility warehouse would not represent a risk to the container or closure or affect the integrity of the sample results. But whether the act of collecting a sample in the warehouse violates the CGMP requirement that containers "be opened, sampled, and sealed in a manner designed to prevent contamination of their contents..." will depend on the purported quality characteristics of the material under sample and the warehouse environment. For containers or closures purporting to be sterile or depyrogenated, sampling should be under conditions equivalent to the purported quality of the material: a warehouse environment would not suffice (see 21 CFR 211.94 and 211.113(b)). This is to preserve the fitness for use of the remaining containers or closures as well as to ensure sample integrity, if they are to be examined for microbial contamination. At a minimum, any sampling should be performed in a manner to limit exposure to the environment during and after the time samples are removed (i.e., wiping outside surfaces, limiting time that the original package is open, and properly resealing the original package). Well-written and followed procedures are the critical elements.

Note that the CGMPs at 21 CFR 211.84 permit a manufacturer to release for use a shipment of containers or closures based on the supplier's certificate of analysis and a visual identification of the containers or closures. Once a supplier's reliability has been established by validation of their test results, a manufacturer could perform the visual examination entirely in the warehouse.

References:

- 21 CFR 211.84: Testing and approval or rejection of components, drug product containers, and closures
- 21 CFR 211.94: Drug product containers and closures
- 21 CFR 211.113(b): Control of microbiological contamination
- 21 CFR 211.122: Materials examination and usage criteria

3. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through 0.2 micron sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?

A firm had multiple media fill failures. The media fill runs, simulating the filling process during production, were conducted inside an isolator. The firm used TSB (nonsterile bulk powder) from a commercial source and prepared the sterile solution by filtering through a 0.2 micron sterilizing filter. An investigation was launched to trace the source of contamination. The investigation was not successful in isolating or recovering the contaminating organism using conventional microbiological techniques, including the use of selective (e.g., blood agar) and nonselective (e.g., TSB and tryptic soy agar) media, and examination under a microscope. The contaminant was eventually identified to be *Acholeplasma laidlawii* by using 16S rRNA gene sequence. The firm subsequently conducted studies to confirm the presence of *Acholeplasma laidlawii* in the lot of TSB used. Therefore, it was not a contaminant from the process, but from the media source.

Acholeplasma laidlawii belongs to an order of *Mycoplasma*. *Mycoplasma* contain only a cell membrane and have no cell wall. They are not susceptible to beta-lactams and do not take up Gram stain. Individual organisms are pleomorphic (assume various shapes from cocci to rods to filaments), varying in size from 0.2 to 0.3 microns or smaller. It has been shown that *Acholeplasma laidlawii* is capable of penetrating a 0.2 micron filter, but is retained by a 0.1 micron filter (see Sundaram, Eisenhuth, et al. 1999). *Acholeplasma laidlawii* is known to be associated with animal-derived material, and microbiological media is often from animal sources. Environmental monitoring of *Mycoplasma* requires selective media (PPLO broth or agar).

Resolution:

For now, this firm has decided to filter prepared TSB, for use in media fills, through a 0.1 micron filter (note: we do not expect or require firms to routinely use 0.1 micron filters for media preparation). In the future, the firm will use sterile, irradiated TSB when it becomes available from a commercial supplier. (Firm's autoclave is too small to permit processing of TSB for media fills, so this was not a viable option.) The firm will continue monitoring for *Mycoplasma* and has revalidated their cleaning procedure to verify its removal. In this case, a thorough investigation by the firm led to a determination of the cause of the failure and an appropriate corrective action.

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.72: Filters
- 21 CFR 211.84(d)(6): Testing and approval or rejection of components, drug product container, and closures
- Sundaram, S, J Eisenhuth, G Howard, and H Brandwein, 1999, Application of Membrane Filtration for Removal of Diminutive Bioburden Organisms in Pharmaceutical Products and Processes, PDA J Pharm Sci Technol, 53(4):186–201
- Kong, F, G James, S Gordon, A Zekynski, and GL Gilbert, 2001, Species-Specific PCR for Identification of Common Contaminant Mollicutes in Cell Culture, Appl Environ Microbiol, 67(7):3195–3200
- Murray, P, E Baron, M Pfaller, F Tenover, and R Tenover, 1995, Manual of Clinical Microbiology, 6th ed., Washington, DC: ASM Press

Date: 5/18/2005

4. Some products, such as transdermal patches, are made using manufacturing processes with higher in-process material reject rates than for other products and processes. Is this okay?

Maybe. It depends on the cause and consistency of the reject rate. Many transdermal patch manufacturing processes produce more waste (i.e., lower yield from theoretical) than other pharmaceutical processes. This should not of itself be a concern. The waste is usually due to the cumulative effect of roll splicing, line start-ups and stoppages, roll-stock changes, and perhaps higher rates of in-process sampling. This is most pronounced for processes involving lamination of rolls of various component layers. Roll-stock defects detected during adhesive coating of the roll, for example, can often only be rejected from the roll after final fabrication/lamination of the entire patch, which contributes to the final process waste stream.

We expect that validated and well-controlled processes will achieve fairly consistent waste amounts batch-to-batch. Waste in excess of the normal operating rates may need (see 21 CFR 21.192) to be evaluated to determine cause (e.g., due to increase in sampling or higher than normal component defects...or both) and the consequences on product quality assessed. We've seen a small number of cases where unusually high intra-batch rejects/losses were due to excessive component quality variability and poorly developed processes.

References:

- 21 CFR 211.100: Written procedures; deviations
- 21 CFR 211.103: Calculation of yield
- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- 21 CFR 211.192: Production record review

5. Do CGMPs require three successful process validation batches before a new active pharmaceutical ingredient (API) or a finished drug product is released for distribution?

No. Neither the CGMP regulations nor FDA policy specifies a minimum number of batches to validate a manufacturing process. The current FDA guidance on APIs (see guidance for industry ICH Q7 for APIs) also does not specify a specific number of batches for process validation.

FDA recognizes that validating a manufacturing process, or a change to a process, cannot be reduced to so simplistic a formula as the completion of three successful full-scale batches. The Agency acknowledges that the idea of three validation batches became prevalent in part because of language used in past Agency guidance. FDA's process validation guidance now recommends a product lifecycle approach. The emphasis for demonstrating validated processes is placed on the manufacturer's process design and development studies in addition to its demonstration of reproducibility at scale, a goal that has always been expected.

However, a minimum number of conformance (a.k.a. validation) batches necessary to validate the manufacturing processes is not specified. The manufacturer is expected to have a sound rationale for its choices in this regard. The Agency encourages the use of science-based approaches to process validation.

In March 2004, FDA revised the Compliance Policy Guide (CPG) Sec. 490.100 on *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*. The CPG describes the concept that, after having identified and establishing control of all critical sources of variability, conformance batches are prepared to demonstrate that under normal

conditions and operating parameters, the process results in the production of an acceptable product. Successful completion of the initial conformance batches would normally be expected before commercial distribution begins, but some possible exceptions are described in the CPG. For example, although the CPG does not specifically mention concurrent validation for an API in short supply, the Agency would consider the use of concurrent validation when it is necessary to address a true short-supply situation, and if the concurrent validation study conforms to the conditions identified in the CPG (see paragraph 4, a-c).

The conditions outlined in the CPG include expanded testing for each batch intended to address a short-supply situation. Expanded testing conducted according to an established validation protocol could provide added assurance that the batch meets all established and appropriate criteria before the API is used in the finished drug product. Additionally, confidence in the API manufacturing process may be gained by enhanced sampling (larger sample size representative of the batch) and perhaps the testing of additional attributes. Validated analytical methods are needed for testing every batch, including validation batches. The Agency would also expect the manufacturer to use a validation protocol that includes a review and final report after multiple batches are completed, even though the earlier batches may have been distributed or used in the finished drug product.

References:

- [21 CFR 211.100](#): Written procedures; deviations
- [21 CFR 211.110](#): Sampling and testing of in-process materials and drug products
- Compliance Policy Guide Sec. 490.100 [Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval](#)
- FDA Guidance for Industry, 2001, [ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients](#)
- FDA Guidance for Industry, 2011, [Process Validation: General Principles and Practices](#)

6. Is it generally acceptable from a CGMP perspective for a manufacturer of sterile drug products produced by aseptic processing to rely solely on ISO 14644-1 and ISO 14644-2 when qualifying its facility?

No. It is generally not acceptable from a CGMP perspective for a manufacturer of sterile drug products produced by aseptic processing to rely solely on ISO [International Organization for Standardization] 14644-1 Part 1: Classification of Air Cleanliness (14644-1) and ISO 14644-2 Part 2: Specifications for Testing and Monitoring to Prove Compliance with ISO 14644-1 (14644-2) when qualifying its facility. Rather, a manufacturer of sterile drug products produced by aseptic processing should use these ISO standards in combination with applicable FDA regulations, guidance, and other relevant references to ensure a pharmaceutical facility is under an appropriate state of control. Consequently, appropriate measures augmenting ISO's recommendations (e.g., with microbiological data) would likely be expected for a firm to meet or exceed CGMP in a pharmaceutical facility. Please understand that 14644-1 and 14644-2 have superseded Federal Standard 209E, Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones (Federal Standard 209E). In November 2001, the U.S. General Services Administration canceled Federal Standard 209E.

Although 14644-1 and 14644-2 are not FDA regulations or FDA guidance, the Agency believes that they are useful in facilitating the international harmonization of industrial air classification for nonviable particle cleanliness in multiple industries (e.g., computer, aerospace, pharmaceutical). As such, FDA adopted these particle cleanliness ratings in the 2004 guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. However, due to the unique aspects of producing sterile drug products by aseptic processing (e.g., microbiological issues), an aseptic processing manufacturer should not rely solely on 14644-1 and 14644-2 when qualifying its facility.

References:

- [U.S. Food and Drug Administration Web site](#)
- [International Organization for Standardization Web site](#)
- ISO 14644-1 Part 1: Classification of Air Cleanliness
- ISO 14644-2 Part 2: Specifications for Testing and Monitoring to Prove Compliance with ISO 14644-1
- FDA Guidance for Industry, 2004, [Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice](#)
- 21 CFR part 211: [Current Good Manufacturing Practice for Finished Pharmaceuticals](#)

7. In 2004, FDA issued a guidance entitled "PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" that encouraged industry to modernize manufacturing through enhancements in process control. How can I implement PAT (Process Analytical Technology)?

The objective of FDA's PAT program is to facilitate adoption of PAT. In our 2004 guidance, we discuss FDA's collaborative approach to promote industry uptake of new and beneficial technologies that modernize manufacturing operations and enhance process control. FDA recognizes that firms should be encouraged to promptly implement new systems that improve assurance of quality and process efficiency. Accordingly, our approach to PAT implementation is risk based and includes multiple options:

- (1) PAT can be implemented under the facility's own quality system. CGMP inspections by a PAT-certified investigator can precede or follow PAT implementation.
 - (2) As another quality system implementation option, FDA invites manufacturers to request a preoperational review of their PAT manufacturing facility and process (see ORA Field Management Directive No.135).
 - (3) A supplement (Changes Being Effected (CBE), CBE-30, or Prior Approval Supplement (PAS)) can be submitted to the Agency prior to implementation, and, if necessary, an inspection can be performed by a PAT-certified investigator before implementation. This option should be used, for example, when an end product testing specification established in the application will be changed.
 - (4) A comparability protocol can be submitted to the Agency outlining PAT research, validation and implementation strategies, and time lines. Following collaborative review of the general strategy outlined in the comparability protocol, the regulatory pathway can include implementation under the facility's own quality system, a preoperational review, CGMP inspections (either before or after PAT implementation), a combination of these, or another flexible approach.
- Manufacturers should evaluate and discuss with the Agency the most appropriate option for PAT implementation (see questions [8](#) and [9](#), below).

References:

- FDA Guidance for Industry, 2004, PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
- ORA Field Management Directive No.135: [Pre-operational Reviews of Manufacturing Facilities](#) Date Revised: 9/16/2013

8. How do I contact CDER with questions about PAT?

Manufacturers should contact the Office of Pharmaceutical Quality and/or the appropriate review division in CDER to discuss applicability of PAT to CDER-regulated products.

Contact for further information:

[CDER Key Officials](#)

Date Revised: 6/18/2015

9. How do I contact CBER with questions about PAT?

Manufacturers should contact the appropriate review division in CBER to discuss applicability of PAT to CBER-regulated products.

Contact for further information:

[CBER Key Staff Directory](#)

Date Revised: 9/16/2013

10. What is the acceptable media fill frequency in relation to the number of shifts? Normally, media fills should be repeated twice per shift per line per year. Is the same frequency expected of a process conducted in an isolator?

A firm's justification for the frequency of media fills in relation to shifts should be risk based, depending on the type of operations and the media fill study design. For *closed*, highly automated systems run on multiple shifts, a firm with a rigorous media fill design may be justified to conduct a lower number of total media fill runs. Such a program can be appropriate provided that it still ensures performance of media fills for each aseptic processing line at least semiannually. The 2004 guidance for industry on *Sterile Drug Products Produced by Aseptic Processing* states that "[A]ctivities and interventions representative of each shift, and shift changeover, should be incorporated into the design of the semi-annual qualification program." In addition, the EU Annex 1, *Manufacture of Sterile*

Medicinal Products, states that "Normally, process simulation tests should be repeated twice a year per shift and process."

Certain modern manufacturing designs (isolators and *closed vial* filling) afford isolation of the aseptic process from microbiological contamination risks (e.g., operators and surrounding room environment) throughout processing. For such *closed* systems,¹ if the design of the processing equipment is robust and the extent of manual manipulation in the manufacturing process is minimized, a firm can consider this information in determining its media fill validation approach. For example, it is expected that a conventional aseptic processing line that operates on two shifts be evaluated twice per year per shift and culminate in four media fills. However, for aseptic filling conducted in an isolator over two shifts, it may be justified to perform fewer than four media fill runs per year, while still evaluating the line semiannually to ensure a continued state of aseptic process control. This lower total number of media fill runs would be based on sound risk rationale and would be subject to reevaluation if contamination issues (e.g., product nonsterility, media fill failure, any problematic environmental trends) occur.

¹ This does not apply to RABS (restricted access barrier systems).

References:

- 21 CFR 211.63: Equipment design, size, and location
- 21 CFR 211.65: Equipment construction
- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.84(c)(3), which states that "Sterile equipment and aseptic sampling techniques shall be used when necessary."
- 21 CFR 211.113(b), which states that "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and any sterilization process."
- FDA Guidance for Industry, 2004, *Sterile Drug Products Produced by Aseptic Processing*
- EU Annex 1, 2003, *Manufacture of Sterile Medicinal Products*

Date: 12/3/2009

11. Why is the FDA concerned about human topical antiseptic drug products?

FDA has identified several incidents of objectionable microbial contamination of topical antiseptic drug products (e.g., alcohol pads or swabs used to prepare the skin prior to an injection). Microbial contamination may be caused by substandard manufacturing practices, and the Agency is concerned about safety risks, such as from infection, associated with this contamination.

Date: 12/21/2011

12. What specific CGMP regulations might be useful to manufacturers of topical antiseptic drug products?

Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act requires all drugs to be manufactured in conformance with CGMP. The CGMP regulations in 21 CFR parts 210 and 211 for finished pharmaceuticals apply equally to over-the-counter (OTC) and prescription (Rx) drug products (see Compliance Policy Guide Sec. 450.100).

The CGMP regulations provide the minimum legal requirements for conducting reliable operations (see 21 CFR part 211). Some relevant CGMP regulations, with a brief description, are given below:

Manufacturing Design and Control: CGMP Requirements and Recommended Guidance for Manufacturers

- **Design manufacturing facilities** (§ 211.42) and processes (see below) to prevent microbial contamination:
 - **For nonsterile drug products**, establish control procedures to monitor output and validate processes to include bioburden testing (§§ 211.110(a)(6)), 211.111) and establish and follow written procedures designed to prevent the introduction of objectionable microorganisms (§ 211.113(a)).
 - **For sterile drug products**, establish and follow written procedures designed to **prevent** microbial contamination (§ 211.113(b)). See the guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*.
- **Conduct process validation studies** to ensure acceptable output (e.g., with topical antiseptics, particularly product microbiological quality) (§ 211.110(a)). Implement and validate needed changes when deficient manufacturing steps, equipment, or raw materials

may be adversely affecting process control. See the guidance for industry *Process Validation: General Principles and Practices*.

- **Ensure that operating procedures** will consistently produce a quality product (§ 211.100). Review and evaluate any deviations or discrepancies documented during manufacturing and testing to determine if a product lacks assurance of sterility (for sterile antiseptics) or may be contaminated with objectionable microorganisms (for nonsterile antiseptics). Document and implement any corrective actions deriving from the evaluation (§ 211.192).
- **Ensure that all equipment**, including water systems, operates consistently and is clean, sanitary, and suitable for its intended use (§§ 211.63, 211.65, 211.67, and 211.68).
- **Establish and follow in-process bioburden testing** procedures to help monitor in-process control, including understanding the bioburden challenge to a final sterilization process (§ 211.110(a)(6)).

Components, In-Process Materials, Containers or Closures, and Finished Product Testing: CGMP Requirements for Manufacturers

- **Establish appropriate written testing standards/specifications and sampling plans** for components, in-process materials, containers or closures, and finished products (§ 211.160).
- **Establish procedures for testing** and approval or rejection of components, drug product containers, and closures (§ 211.80). Test each lot of a drug product component and container or closure, including those that may be vulnerable to microbiological contamination (§ 211.84)(d)(4-5), including applicator material (e.g., cotton pads) and water used as an ingredient in the product.
- **Conduct appropriate microbiological tests** before a batch disposition decision is made. Test each batch of a sterile product for sterility (§ 211.167). Test each batch of a non-sterile product to ensure absence of objectionable microorganisms (§ 211.165(b)).

Management

The CGMPs require that the management of a manufacturing facility maintains a well-functioning quality system, which includes an effective quality unit vested with the responsibilities and authorities required under CGMP (§ 211.22). See ICH guidances for industry *Q9 Quality Risk Management* and *Q10 Pharmaceutical Quality System*.

References:

- Compliance Policy Guide Sec. 450.100 [CGMP Enforcement Policy—OTC vs Rx Drugs](#)
- 21 CFR part 211: [Current Good Manufacturing Practice for Finished Pharmaceuticals](#)
- FDA Guidance for Industry, 2004, [Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice](#)
- FDA Guidance for Industry, 2011, [Process Validation: General Principles and Practices](#)
- FDA Guidance for Industry, 2006, [ICH Q9 Quality Risk Management](#)
- FDA Guidance for Industry, 2009, [ICH Q10 Pharmaceutical Quality System](#)

Date: 12/21/2011

13. How can manufacturers assess and address the risk of microbiological contamination of topical antiseptics?

Because there are potentially many different root causes of product contamination by microorganisms, it is imperative that manufacturers perform a manufacturing risk assessment to understand manufacturing failure modes and implement prevention measures.

In addition, any risk assessment approach should be informed by an understanding of the microbial contamination vulnerabilities of the concerned product. For example, some product considerations for manufacturers include, but are not limited to:

- Determine the types of microbes that might survive or thrive in your products. Provide additional controls and testing based on the output of the risk assessment to ensure product quality.
- Ensure that your microbial recovery methods are capable of detecting the types of microbes that may affect product quality.
- Evaluate risk of contamination from components, including during component production, storage, or due to the intrinsic risk from source materials. Consider all possible sources of microbial contamination, including the following:

- Components or products stored in open bins can be at risk for contamination by spore-forming microbes, such as *Bacillus cereus*, as well as by *Serratia* species and other worrisome airborne microbes (see the FDA news release and *Morbidity and Mortality Weekly Report*, referenced below). Manufacturing areas exposed to windy or poor HVAC conditions may increase the potential for this environmental contamination risk.
- Some materials, especially from natural sources, may have high or objectionable intrinsic bioburden.
- Water quality can pose a significant risk, as most antiseptics include water as a key ingredient. Contaminated purified water has been the root cause of multiple recalls of antiseptics, including instances of antiseptics contaminated with *Burkholderia* (previously *Pseudomonas*) *cepacia*, an opportunistic pathogen.
- Unsanitary practices or sources.
- When manufacturing in areas with high humidity, molds can be of special concern.

References:

- FDA News Release, 2011, [FDA Reminds Health Care Professionals About Safe Use of Non-Sterile Alcohol Prep Pads](#)
- Centers for Disease Control and Prevention, 2011, [Contamination of Alcohol Prep Pads with *Bacillus cereus* Group and *Bacillus* Species](#), *Morbidity and Mortality Weekly Report*, 60(11):347

Date: 12/21/2011

14. Can *Leptospira* species penetrate sterilizing-grade filters? If so, what should manufacturers keep in mind in their ongoing lifecycle risk management efforts to ensure microbial control?

FDA is aware of a report of *Leptospira licerasiae* contamination in cell cultures (see Chen, Bergenvin, et al. 2012). There is no indication that this bacterium ultimately contaminated either the finished drug substance or drug product. This bacterium has been found to pass through 0.1 µm pore size rated sterilizing-grade membrane filters. While this specific species was the identified contaminant in this case, other *Leptospira* species also are capable of passing through 0.1 µm pore size rated filters (see Faine 1982). Compendial microbiological test methods typically used in association with upstream biotechnology and pharmaceutical production are not capable of detecting this type of bacteria. Whether this apparently rare contamination risk may be more widespread is unknown, and we are sharing this information so that manufacturers can consider whether this hazard may be relevant to their operations.

Leptospira are Gram-negative aerobic spirochetes that are flexible, highly motile, and spiral-shaped with internal flagella. The bacteria measure 1µm in diameter and 10-20 µm in length. *Leptospira* are obligate aerobes that use oxygen as the electron receptor and long-chain fatty acids as a major source of energy. While some of the *Leptospira* are harmless fresh-water saprophytes, other species are pathogenic and can cause leptospirosis, a significant disease in humans and animals (Ricaldi, Fouts, et al. 2012; Matthias, Ricaldi, et al. 2008; Bharti, Nally, et al. 2003). Based on current information, *Leptospira* contamination does not appear to occur frequently, and purification steps that follow cell culture in a typical biotechnology operation would be expected to prevent carryover to the finished drug substance. Testing of bulk drug substances produced in the reported cases did not detect the *Leptospira* species, and no evidence of deleterious effects on in-process product were observed in the known case study. However, we are providing this communication to alert manufacturers that these types of bacteria can potentially:

- Penetrate sterilizing-grade membrane filters
- Be present in the manufacturing site environment
- Impact in-process production (e.g., production yields, impurity levels, process performance)
- Go undetected due to the limitations of current compendial bioburden tests in detecting this microbial genus

As a general principle, manufacturers should use sound risk management and be aware of unusual microbiota reported in the literature that may impact their manufacturing processes (e.g., cell culture biotechnology, conventional sterile drug manufacturing). Manufacturers should assess their operations, be aware of potential risks, and apply appropriate risk management based on an understanding of possible or emerging contamination risks (see section 18.3 in ICH guidance for

industry Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients). As appropriate, preventive measures should be implemented during the product and process lifecycle.

To illustrate, if leptospiral contamination is considered possible, or has occurred, risk mitigation procedures and practices for this microorganism should include at least the following:

- (1) Review of available published articles from the scientific literature and technical reports by related industry organizations that may provide further understanding on how to mitigate this contamination hazard.
- (2) Use of molecular or nonconventional microbial monitoring methods at appropriate intervals to detect microbial flora that may exist in processing steps or in the immediate environment, but are not readily detected by current routine methods. Such expanded testing should be used to modify the strategy (e.g., timing, frequency, types of tests) of detection and control in the event of newly identified risk posed by the viable, but not easily cultured, microorganism. Examples include: a. Use of specialized media such as Ellinghausen McCullough Johnson Harris (EMJH) medium (Ellinghausen and McCullough 1965) or other suitable media (Rule and Alexander 1986). It should be noted that these bacteria typically grow very slowly. b. Use of validated polymerase chain reaction (PCR) methods (e.g., as an investigative tool) for rapid screening and detection of spirochete bacteria. c. Consideration of special stain techniques or other means to identify the presence of *Leptospira* (Frank and Kohn 1973).
- (3) Use of conventional approaches. Firms should continue to properly employ basic, standard microbiology laboratory practices to detect contamination. For example, the laboratory should ensure that microscopic examination is part of its routine cell culture process control program, as it provides an important means of detecting microbial contaminants that may not readily grow on conventional media.
- (4) Implementing such quality risk-management measures into the initial design (i.e., preventive actions) and promptly implementing an appropriate corrective action plan in response to newly identified contamination sources, throughout the life cycle of the product.

References:

- FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
- Chen, J, J Bergenvin, R Kiss, G Walker, T Battistoni, P Lufburrow, H Lam, and A Vinther, 2012, Case Study: A Novel Bacterial Contamination in Cell Culture Production—*Leptospira licerasiae*, PDA J Pharm Sci Technol, 66(6):580–591
- Faine, S (ed.), 1982, Guidelines for the Control of Leptospirosis, Geneva: World Health Organization
- Ricaldi, JN, DE Fouts, JD Selengut, DM Harkins, KP Patra, et al., 2012, Whole Genome Analysis of *Leptospira licerasiae* Provides Insight into Leptospiral Evolution and Pathogenicity, PLoS Negl Trop Dis, 6(10):e1853
- Matthias, MA, JN Ricaldi, M Cespedes, MM Diaz, RL Galloway, et al., 2008, Human Leptospirosis Caused by a New Antigenically Unique *Leptospira* Associated with a *Rattus* Species Reservoir in the Peruvian Amazon, PLoS Negl Trop Dis, 2(4):e213
- Bharti, AR, JE Nally, JN Ricaldi, MA Matthias, MM Diaz, et al., 2003, Leptospirosis: A Zoonotic Disease of Global Importance, Lancet Infect Dis, 3:757–771
- Ellinghausen, HC, and WG McCullough, 1965, Nutrition of *Leptospira pomona* and Growth of 13 Other Serotypes: Fractionation of Oleic Albumin Complex (OAC) and a Medium of Bovine Albumin and Polysorbate 80, Am J Vet, 26:45–51
- Rule PI, and AD Alexander, 1986, Gellan Gum as a Substitute for Agar in Leptospiral Media, J Clin Microbiol, 23(3):500–504
- Frank S, and J Kohn, 1973, J Amer Med Technology, July–Aug

Date: 12/20/2012

15. FDA withdrew its draft guidance for industry on *Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment*. What were the Agency’s major concerns with this guidance?

FDA's major concern was that sections V and VII of the withdrawn draft guidance no longer represented the Agency's current thinking, as explained below. Section V (Exhibit/Validation Batch Powder Mix Homogeneity) recommended that at least 3 replicate samples be taken from at least 10 locations in the powder blender, but that only 1 of the 3 replicates be evaluated to assess powder blend uniformity. The Agency currently recommends that *all* replicate samples taken from various locations in the blender be evaluated to perform a statistically valid analysis. This analysis can demonstrate that variability attributable to sample location is not significant and that the powder blend is homogenous. Statistical tools are available to ascertain both the number of replicates and the number of sampling locations across the blender that should be analyzed to conduct a valid analysis. Section VII (Routine Manufacturing Batch Testing Methods) acceptance criteria designated to the Standard Criteria Method and the Marginal Criteria Method were based upon the limits published in the United States Pharmacopeia (USP) General Chapter <905> *Uniformity of Dosage Units*. However, the procedures and acceptance criteria in General Chapter <905> are not a statistical sampling plan and so the results of the procedures should not be extrapolated to larger populations. Therefore, because the procedure and acceptance criteria prescribed in section VII provided only limited statistical assurance that batches of drug products met appropriate specifications and statistical quality control criteria, FDA no longer supports their use for batch release. Currently, there are several standard statistical practices that, if used correctly, can help to ensure compliance with CGMP regulations, including 21 CFR 211.110, 21 CFR 211.160, and 21 CFR 211.165.

References:

- 21 CFR 211.110: [Sampling and testing of in-process materials and drug products](#)
- 21 CFR 211.160: [General requirements \[Laboratory Controls\]](#)
- 21 CFR 211.165: [Testing and release \[of the finished drug product\] for distribution](#)

Date: 8/6/2013

16. Why is FDA concerned about proper sampling of powder blends?

The CGMPs require that all sampling plans be scientifically sound and representative of the batch under test (see 21 CFR 211.160(b)). Further, in-process testing of powder blends to demonstrate adequacy of mixing is a CGMP requirement (21 CFR 211.110). Between- and within-location variability in the powder blend is a critical component of finished product quality and therefore should be evaluated. Drug product manufacturers need to use a science- and risk-based sampling approach to ensure (a) adequacy of blend mixing and (b) that sampling of the blend is done at a suitable juncture in the manufacturing process. The sampling and analysis needs to ensure that no differences exist between locations in a blend that could adversely affect finished product quality. Traditional sampling using a powder-thief may have drawbacks and limitations, such as causing disturbance to the powder bed, powder segregation, or other sampling errors. However, powder-thief sampling remains widely used and provides reliable results in many cases. The Agency encourages firms to adopt more innovative approaches to ensuring adequacy of mixing (see, e.g., the guidance for industry *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*). If a manufacturer proposes to use a thief sampling method, the reliability of the method should be evaluated as part of analytical methods development.

References:

- FDA Guidance for Industry, 2004, [PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance](#)

Date: 8/6/2013

17. What are some recommended innovative approaches to ensuring adequacy of mixing of powder blends?

Innovative approaches to consider include, but are not limited to:

- (a) PAT real-time monitoring and feed-forward controlling of the powder blending process (see the guidance for industry *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*) and
- (b) use of statistical process control tools to monitor the powder blending process and to maintain a state of control.

When a manufacturer decides to implement PAT or other process-monitoring and control techniques for powder blend homogeneity assessment, its decision should be supported with appropriate data and rationale using a science- and risk-based approach. For example, the effective sample size of powder examined by PAT probes has to be estimated such that the scale of scrutiny of the PAT powder blending monitoring can be justified (Wu, Tawakkul, et al. 2009). The number of PAT probes and their locations also have to be justified. If a scientifically sound PAT monitoring and control strategy is established, it can facilitate the assessment of (a) variability across locations within the powder bed (El-Hagrasy, Morris, et al. 2001), (b) variability over time of one location, and (c) potential correlation between the powder sample and the unit dosage form.

References:

- FDA Guidance for Industry, 2004, [PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance](#)
- Wu, H, M Tawakkul, M White, and M Khan, 2009, Quality-by-Design (QbD): An Integrated Multivariate Approach for the Component Quantification in Powder Blends, *International Journal of Pharmaceutics*, 372(1-2):39–48
- El-Hagrasy, A, H Morris, F D’Amico, et al., 2001, Near-Infrared Spectroscopy and Imaging for the Monitoring of Powder Blend Homogeneity, *Journal of Pharmaceutical Sciences*, 90(9):1298–1307

Date: 8/6/2013

18. What are the Agency’s recommendations regarding in-process stratified sampling of finished dosage units?

Stratified sampling is recommended to be used when the population is known to have several subdivisions (i.e., locations), which may give different results for the quality characteristics measured. The Agency expects that no significant differences should exist between in-process locations that could affect finished product quality. Between- and within-location variability is a critical component of finished product quality and therefore should be evaluated. Please refer to ASTM E2709 and ASTM E2810 for further guidance on establishing acceptance criteria for a stratified sampling plan.

References:

- ASTM Standard E2709, 2014, Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure, West Conshohocken, PA: [ASTM International](#)
- ASTM Standard E2810, 2011, Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units, West Conshohocken, PA: [ASTM International](#)

Date: 8/6/2013

19. For a nonsterile compendial drug product that includes an antimicrobial preservative in its formulation, may I release and market lots of this drug product with initial out-of-specification total aerobic plate counts if these lots test within specification 2 weeks later?

No. 21 CFR 211.113(a) requires appropriate written procedures to be established and followed during manufacturing to prevent objectionable microorganisms in drug products not required to be sterile. Additionally, the second paragraph of USP General Chapter <51> Antimicrobial Effectiveness Testing reads: Antimicrobial preservatives should not be used as a substitute for good manufacturing practices, solely to reduce the viable microbial population of a nonsterile product, or control the presterilization bioburden of a multidose formulation during manufacturing. Drug manufacturers should not rely on antimicrobial preservatives to reduce initial out-of-specification plate counts to within-specification levels and then market the product. Section 211.165(f) mandates that drug products failing to meet established standards or specifications be rejected. The initial test results exhibiting out-of specification levels of microbes are not disqualified even if subsequent test results are within specifications. In such cases, FDA still expects the manufacturer to reject the drug product based on the initial results. It is also not acceptable for manufacturers to allow an inappropriately long time (e.g., weeks) to pass before testing the product, which might permit the preservative to reduce levels of microbes possibly introduced during manufacture and thus avoid out-of-specification test results. Finally, drug manufacturers should review their manufacturing process to determine

procedures or equipment that might introduce contaminating microorganisms into the process or product.

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.165: Testing and release for distribution
- USP 38–National Formulary (NF) 33 (2015) General Chapter <51> Antimicrobial Effectiveness Testing
- USP 38–NF 33 (2015) General Chapter <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests
- USP 38–NF 33 (2015) General Chapter <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms

Date: 6/11/2015

20. Do pharmaceutical manufacturers need to have written procedures for preventing growth of objectionable microorganisms in drug products not required to be sterile? What does *objectionable* mean anyway?

Yes, CGMP regulations do require these written procedures. 21 CFR 211.113(a) specifies that appropriate written procedures be established and followed to prevent growth of objectionable microorganisms in drug products not required to be sterile. Even though a drug product is not sterile, a firm must follow written procedures that proactively prevent introduction and proliferation of objectionable microorganisms. 21 CFR 211.165(b) states that “[t]here shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms” before it is released for distribution. The meaning of the term *objectionable* needs to be evaluated on a case-by-case basis by each drug manufacturer. The primary meaning relates to microbial contaminants that, based on microbial species, numbers of organisms, dosage form, intended use, patient population, and route of administration, would adversely affect product safety. Microorganisms may be objectionable for several reasons; for example, they:

- Are a known human pathogen
- Adversely affect product stability
- React with, or potentially damage the integrity of, the container closure system (for example, fermentation that creates gaseous pressures sufficient to rupture a product container/closure)
- Interfere with analytical methods or active ingredient bioavailability

Establishing production time limits is an example of a control to prevent growth of objectionable microorganisms. Per 21 CFR 211.111, time limits for the completion of each phase of production, when appropriate, must be established and followed. For example, if a firm finds it necessary to hold a bulk topical or liquid product for several months until it is filled, the firm might establish a holding time limit to help prevent objectionable microbial buildup. Validation and control over microbial content of purified water systems used in certain topical products are also examples of such procedures (see FDA guidance, referenced below).

References:

- 21 CFR 211.113: Control of microbiological contamination
- 21 CFR 211.165: Testing and release for distribution
- 21 CFR 211.111: Time limitations on production
- FDA Guidance for Industry, 2011, Process Validation: General Principles and Practices

Date: 6/11/2015

21. For drug products formulated with preservatives to inhibit microbial growth, is it necessary to test for preservatives as part of batch release and stability testing?

Yes. Two types of tests are generally used. Initially, firms perform antimicrobial preservative effectiveness testing to determine a minimally effective level of preservative. Once that level has been determined, firms may establish appropriate corresponding analytical test specifications. Firms may then apply the analytical tests for preservative content at batch release and throughout the shelf life of lots on stability.

References:

- 21 CFR 211.165: Testing and release for distribution
- 21 CFR 211.166: Stability testing
- USP 38–NF 33 (2015) General Chapter <51> Antimicrobial Effectiveness Testing

Date: 6/11/2015

Contact for further information: CDER-OPQ-Inquiries@fda.hhs.gov

4.6. Holding and Distribution

1. What is a recall?

Recalls are actions taken by a firm to remove from the market any product that is in violation of laws administered by FDA. Recalls of a drug may be conducted on a firm's own initiative or by FDA request. A recall is an alternative to an FDA-initiated court action for removing or correcting violative, distributed products (see 21 CFR 7.40(a)). Under FDA's CGMP regulations for finished pharmaceuticals, manufacturers must establish and follow written procedures to facilitate the recall of defective products from the market (see 21 CFR 211.150(b)).

References:

- 21 CFR 7.40(a): Recall policy
- 21 CFR 211.150(b): Distribution procedures

Date: 8/9/2010

2. Can FDA mandate a recall of human drugs?

FDA does not have authority to mandate a recall of a human drug, but it can take more authoritative legal actions against manufacturers that persist in marketing a defective product, such as seizure and injunction. A recall is a firm's removal or correction of a marketed product that FDA considers to be in violation of the laws it administers, and against which FDA would otherwise initiate more powerful legal action (see 21 CFR 7.40(c); also see chapter 7 in FDA's Investigations Operations Manual). Thus, manufacturers typically initiate voluntary recalls when a defect is found within a marketed batch to avoid a potentially more significant enforcement action by FDA. References:

- 21 CFR 7.40(c): Recall policy
- FDA, 2014, Chapter 7—Recall Activities, [Investigations Operations Manual](#)

Date: 8/9/2010

3. Are over-the-counter (OTC) drugs subject to the same recall provisions as prescription drugs?

Yes, FDA's recall expectations for drugs apply equally to OTC and prescription. The CGMP regulations also apply to all drug products, whether OTC or prescription.

Reference:

- Compliance Policy Guide Sec. 450.100 [CGMP Enforcement Policy—OTC vs Rx Drugs](#)

Date: 8/9/2010

4. Do manufacturers of OTC products have to report quality defects?

Manufacturers of OTC drugs approved in a new drug application are required to report quality defects (see 21 CFR 314.81). Manufacturers or distributors of OTC monograph drugs (these are drugs that are not approved in a product-specific application) are not required to submit quality defect reports. However, the manufacturer, packer, or distributor whose name appears on the label of an OTC drug without an approved application (i.e., OTC monograph drugs) must submit to FDA any report received of a serious adverse event associated with such drug when used in the United States (see section 760 of the Federal Food, Drug, and Cosmetic Act). Thus, if a serious adverse event is caused by a quality defect, FDA will receive a report about the event (see also the guidance for industry Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application).

References:

- 21 CFR 314.81: Other postmarketing reports
- Federal Food, Drug, and Cosmetic Act, section 760
- FDA Guidance for Industry, 2009, [Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application](#)

Date: 8/9/2010

5. Does FDA expect firms to investigate both released and rejected lots for potential recalls?

Yes. Under 21 CFR 211.180(e), manufacturers must establish and follow written procedures for periodically reviewing complaints, recalls, returned or salvaged drug products, and investigations of product discrepancies. Firms must also review an appropriate number of batches, whether approved or rejected, and, where applicable, records associated with the batches, to ensure that all potentially affected product is thoroughly investigated and appropriate follow-up action is taken (21 CFR 211.192).

References:

- 21 CFR 211.180(e): General requirements
- 21 CFR 211.192: Production record review

Date: 8/9/2010

6. What happens if a firm does not voluntarily recall a defective product?

FDA expects that a firm will voluntarily recall a drug that is defective or flawed if it could be hazardous to health. Seizure, multiple seizure, or other court action is indicated when a firm refuses to undertake a recall requested by FDA, or where the Agency has reason to believe that a recall would not be effective, determines that a recall is ineffective, or discovers that a violation is continuing (21 CFR 7.40(c)).

References:

- 21 CFR 7.40(c): [Recall policy](#)

Date: 8/9/2010

Contact for further information:CDER-OPQ-Inquiries@fda.hhs.gov**4.7. Laboratory Controls****1. Many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be?**

The auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check (21 CFR 211.68). For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step. Note that all batches of a product manufactured between two successive verifications would be affected should the check of the auto-calibrator reveal a problem. Additionally, the calibration of an auto-calibrator should be periodically verified—a common frequency is once a year—using National Institute of Standards and Technology (NIST)-traceable standards or NIST-accredited standards in use in other countries.

References:

- 21 CFR 211.68: Automatic, mechanical, and electronic equipment
- 21 CFR 211.160(b)(4): General requirements (Laboratory Controls)

- United States Pharmacopeia (USP) General Chapter <41> Weights and Balances
- See also ASTM standard E 617, 2013, Standard Specification for Laboratory Weights and Precision Mass Standards, West Conshohocken, PA: [ASTM International](#) (This standard is incorporated into the USP by reference; other widely recognized standards may be acceptable)

2. Do CGMPs require that forced degradation studies always be conducted of the drug product when determining if a drug product stability test method is stability indicating?

No. Drug product stress testing (forced degradation) may not be necessary when the routes of degradation and the suitability of the analytical procedures can be determined through use of the following:

- Data from stress testing of the drug substance
- Reference materials for process impurities and degradants
- Data from accelerated and long-term studies on the drug substance
- Data from accelerated and long-term studies on the drug product

Additional supportive information on the specificity of the analytical methods and on degradation pathways of the drug substance may be available from literature sources. Section 211.165(e) of the CGMP regulations states that the accuracy, sensitivity, specificity, and reproducibility of test methods shall be established and documented (21 CFR 211.165(e)). Further, 21 CFR 211.166(a)(3) requires that stability test methods be reliable, meaningful, and specific, which means that the content of the active ingredient, degradation products, and other components of interest in a drug product can be accurately measured without interference, often called *stability indicating*. The CGMP regulations do not specify what techniques or tests are to be used to ensure that one's test methods are stability indicating. However, evaluating the specificity of the test methods during forced degradation studies (i.e., exposing the drug to extremes of pH, temperature, oxygen, etc.) of the drug substance and drug product often is necessary to ensure that stability test methods are stability indicating. But in certain circumstances, conducting a forced degradation study of just the drug substance may be sufficient to evaluate the stability-indicating properties of a test method. Generally, in determining whether it is necessary to conduct forced degradation studies of the drug product, the specificity of the test method should be evaluated for its ability to assay drug substance, degradants, and impurities, in the presence of each other, without interference. The evaluation also should provide assurance that there is not a potential for interaction between the drug substance, degradants, impurities, excipients, and container-closure system during the course of the shelf life of the finished drug product. Last, the rationale for any decision made concerning the extent of the forced degradation studies conducted as well as the rationale for concluding that a test method is stability indicating should be fully documented.

References:

- 21 CFR 211.137: Expiration dating
- 21 CFR 211.165(e): Testing and release for distribution
- 21 CFR 211.166(a)(3): Stability testing
- Compliance Policy Guide Sec. 480.100 Requirements for Expiration Dating and Stability Testing (CPG 7132a.04)

3. When performing the USP General Chapter <788> *Particulate Matter in Injections* test for a large volume parenteral (LVP), is it acceptable to take the average among the units tested to determine if the batch meets its specification for this attribute?

No. It is not acceptable to take the average among the LVP units tested in each batch/lot when following this method because the purpose of this method is to measure and limit intra-batch variability.

Particulate matter refers to small, subvisible particles. General Chapter <788> provides two tests for detecting such particulates—light obscuration and microscopic assay. Both are generally accepted for use in testing LVPs and small volume parenterals (SVP) for the determination of subvisible particulate matter. Normally, samples are first tested by the light obscuration method; if the sample fails the specified limits, the microscopic assay method can then be used. However, the microscopic method

can be the sole test if there is a documented technical reason or interference from the product under test that would make the light obscuration method unsuitable or the results invalid.

Confusion about when averaging data is and is not acceptable is probably due to the sample preparation method for the light obscuration test (General Chapter <788>). At least 2, 5-mL aliquots from each sampled unit or the pooled sample (see below) are to be used in the particulate count determination, and the results from these aliquots are to be averaged for comparison with the specification. Note that the average is of the results from examining each aliquot and not between units. (The results of the first aliquot examined by light obscuration are to be discarded, and the subsequent aliquots—2 or more—are retained.) Pooling units prior to analysis is permitted only if the volume in each unit is less than 25 mL, in which case 10 or more units may be pooled. If the volume in the SVP or LVP is 25 mL or more per unit, single units are to be examined by this method (General Chapter <788>).

Results **among** the test units cannot be averaged because particulate matter is assumed to be non-uniformly dispersed throughout the lot. The intent of assessing results from each individual unit is to ensure adequate representation of the lot and to detect potential variation within a lot.

As to the number of individual units to be tested for LVP and SVP units having a volume of 25mL or more, the USP states that the number of units tested depends on "statistically sound sampling plans," and "sampling plans should be based on consideration of product volume, numbers of particles historically found to be present in comparison to limits, particle size distribution of particles present, and variability of particle counts between units." The USP also suggests that the total number of units tested for any given batch may be less than 10 units (for LVP and pooled SVPs) with proper justification. This is consistent with the CGMP requirement for statistical sampling plans (see 21 CFR 211.165).

References:

- 21 CFR 211.160: General requirements (Laboratory Controls)
- 21 CFR 211.165(c)(d): Testing and release for distribution
- USP General Chapter <788> Particulate Matter in Injections
- FDA Guidance for Industry, 2006, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

4. Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness?

Yes. Since the publication of the inspection guide on cleaning validation in 1993, a number of studies have been published to demonstrate the adequacy of TOC in measuring contaminant residues. We think TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation. But in order for TOC to be functionally suitable, it should first be established that a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions. This is not a trivial exercise because we know that some organic compounds cannot be reliably detected using TOC.

TOC use may be justified for direct surface sample testing as well as indirect (rinse water) sample testing. In either case, because TOC does not identify or distinguish among different compounds containing oxidizable carbon, any detected carbon is to be attributed to the target compound(s) for comparing with the established limit. Thus, a firm should limit background carbon (i.e., carbon from sources other than the contaminant being removed) as much as possible. The established limit, or the amount of residue detected for comparison to the specification, should correct for the target material's composition of carbon. As for any cleaning method, recovery studies are necessary (21 CFR 211.160(b)). If TOC samples are being held for long periods of time before analysis, a firm should verify the impact of sample holding time on accuracy and limit of quantitation.

References:

- 21 CFR 211.67: Equipment cleaning and maintenance
- 21 CFR 211.160(b): General requirements (Laboratory Controls)
- USP General Chapter <643> Total Organic Carbon
- [FDA Guide to Inspections: Validation of Cleaning Processes](#)

5. Would a paramagnetic or laser oxygen analyzer be able to detect all possible contaminants or impurities in a medical gas?

No. Although paramagnetic and laser oxygen analyzers are very accurate and reliable when calibrated correctly, these types of analyzers can only detect the presence and measure the strength of oxygen. They are unable to detect contaminants or impurities that may be present, such as hydrocarbons or arsenic compounds. The USP monograph test for oxygen does not include an impurity screen, and other analyzers may need to be used. For example, assays for hydrocarbon impurities are routinely conducted during the oxygen manufacturing process even though the USP does not list hydrocarbons as an impurity. Also, alternative methods may be needed to test high-pressure cylinders for cleaning solution residues.

References:

- 21 CFR 211.160: General requirements (Laboratory Controls)
- 21 CFR 211.165: Testing and release for distribution
- USP Monograph: Oxygen
- USP Monograph: Oxygen 93 Percent

6. Can up to 12-month expiration dating be assigned to oral solid and liquid dosage forms repackaged into unit-dose containers based on guidance in the May 2005 draft revision of Compliance Policy Guide Sec. 480.200 *Expiration Dating of Unit Dose Repackaged Drugs (CPG 7132b.11)*?

No. In May 2005, a Notice of Availability of the draft revision of FDA's Compliance Policy Guide Sec. 480.200 *Expiration Dating of Unit-Dose Repackaged Drugs (CPG 7132b.11)* was announced in the *Federal Register*. The draft CPG specifies certain conditions when it may be possible to assign up to 12-month expiration dating to nonsterile solid and liquid oral drug products repackaged into unit-dose containers without conducting new stability studies to support the length of expiration dating on the repackaged products. The draft CPG was prompted by USP standards for assigning up to a 12-month *beyond-use date* to nonsterile solid and liquid oral dosage forms dispensed in unit-dose containers. (*Beyond-use date* is USP's pharmacy dispensing term for specifying a date on a prescription container beyond which a patient should not use the product.) If finalized, FDA's draft CPG would replace the current version of CPG Sec. 480.200. The current version of CPG Sec. 480.200 was finalized in March 1995 and provides conditions under which FDA will not initiate action for assigning up to 6-month expiration dating for drug products repackaged into unit-dose containers without conducting new stability studies.

FDA is conducting a stability study of certain commercially repackaged drugs to determine the suitability of the draft revision of CPG Sec. 480.200. Until the stability study is complete and FDA evaluates all comments submitted to the public docket in response to the May 2005 *Federal Register* Notice of Availability, the Agency does not intend to make a final decision on the draft revision of CPG Sec. 480.200. Consequently, at this time and until FDA announces a final decision on the draft CPG, the current CPG Sec. 480.200, which was finalized in March 1995, is in effect.

References:

- Compliance Policy Guide Sec. 480.200 *Expiration Dating of Unit Dose Repackaged Drugs (CPG 7132b.11)*
- Draft Guidance on *Expiration Dating of Unit-Dose Repackaged Drugs; Availability* (70 FR 30953, May 31, 2005)
- 21 CFR 211.137: Expiration dating
- 21 CFR 211.166: Stability testing

7. Is it ever appropriate to use an unvalidated method to test a drug component or product?

The CGMP regulations require the use of validated methods when performing routine testing of raw material, in-process material, and finished products (21 CFR 211.160, 211.165(e), and 211.194) for manufacturing finished drug products. Method validation studies establish proof that a method is

suitable for its intended purpose. The purpose is generally to measure a particular material's conformance to an established specification (see the ICH guidance for industry *Q2 (R1) Validation of Analytical Procedures: Text and Methodology*). FDA recognizes, however, that test methods developed based on scientifically sound principles (e.g., sufficient accuracy and precision) but that are not fully validated may be suitable for use in certain instances during an investigation of a potential quality problem or defect. For example, investigation of an atypical impurity or possible contaminant of a drug product or any of its components (e.g., oversulfated chondroitin sulfate in heparin) may indicate the need for additional methods beyond routine quality control tests. Such testing may be critical to promptly and adequately evaluate the problem and protect public health. Full evaluation of a method's robustness and reproducibility may not initially be feasible or appropriate when conducting tests in certain investigations. When a company, for whatever reason, tests drug components or products using an unvalidated method, it is important to recognize the possibility of greater uncertainty in the test results derived from these unvalidated test methods, as compared to validated test methods. Nevertheless, the resulting data may yield important information indicating the need for prompt corrective action. Accordingly, we expect all such test results on drug components or products to be reviewed to assess the need for follow-up action (21 CFR 211.192 and 211.180(e)).

References:

- [21 CFR part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General](#)
- [21 CFR part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals](#)
- [FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients](#)
- [FDA Guidance for Industry, 1995–1996, ICH Q2 \(R1\) Validation of Analytical Procedures: Text and Methodology](#)

Date: 1/6/2011

8. Did FDA withdraw the 1987 Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices?

Yes, FDA withdrew the 1987 Guideline. The 1987 Guideline is considered obsolete and does not reflect the Agency's current thinking on the topic.

Date: 7/12/2011

9. Where can drug manufacturers find information regarding endotoxin testing?

USP publishes endotoxin testing recommendations and acceptance criteria in USP General Chapter <85> *Bacterial Endotoxins Test*. General Chapter <85> provides methods and calculation of limits for drugs. FDA may, as needed, provide additional guidance to clarify the Agency's current thinking on use of Limulus Amebocyte Lysate (LAL), recombinant LAL, and other endotoxin testing methods.

References:

- USP General Chapter <85> Bacterial Endotoxins Test

Date 7/12/2011

10. Is it acceptable to release non-penicillin finished drug products to market if the products may have been exposed to penicillin, as long as the non-penicillin products are tested and no penicillin residue is found?

21 CFR 211.176, Penicillin Contamination, allows marketing of non-penicillin finished drug products if they are tested using the codified method and found not to be contaminated with penicillin. However, it is not acceptable to release the product unless all other applicable CGMP requirements have been met. In some cases, firms inappropriately apply § 211.176 to market products that have not been produced under CGMP. Notably, 21 CFR 211.42(d) requires that manufacturing operations for penicillin drug products be performed in facilities separate from those used for non-penicillin human drug products. Similarly, 21 CFR 211.46(d) requires that air-handling systems for penicillin and non-penicillin drug products be completely separate. For example, if a non-penicillin product is made in a facility that shares equipment or an air-handling system with a penicillin production area (in violation of § 211.46(d)), the non-penicillin product cannot be made CGMP-compliant through testing alone.

However, if a door is accidentally left open between a penicillin-dedicated area and other separate production areas, resulting in possible exposure of the other areas to penicillin, testing those other products for penicillin could justify their release for distribution. However, as per 21 CFR 211.165, all sampling plans and acceptance criteria used for testing and release of the non-penicillin product, including any testing for penicillin contamination, must be adequate to ensure the tested product meets all of its specifications.

References:

- 21 CFR 211.176: Penicillin contamination
- 21 CFR 211.42(d): Design and construction features
- 21 CFR 211.46(d): Ventilation, air filtration, air heating and cooling
- 21 CFR 211.165: Testing and release for distribution

Date: 6/17/2015

11. Can a facility that produced penicillin dosage forms be decontaminated and renovated for production of non-penicillin dosage forms, provided there is no further penicillin production in the renovated facility?

Yes; however, decontamination can be extremely difficult. The decontamination process must include scientifically sound studies demonstrating the efficacy of the decontamination agents, extensive and statistically appropriate sampling throughout the areas before and after decontamination to verify cleanliness, and appropriate testing of such samples with a validated analytical method having an appropriate limit of detection. The CGMP regulations in 21 CFR 211.176 require that if a reasonable possibility exists that a non-penicillin drug product has been exposed to cross contamination with penicillin, the non-penicillin product must be tested for the presence of penicillin and cannot be marketed if detectable levels are found using the codified method. Such a reasonable possibility may be present if decontamination has not been conducted effectively. Although CGMP regulations do not prohibit decontamination and conversion, the difficulty of cleaning up penicillin residues can make the process daunting (see also FDA Guide to Inspections, referenced below).

References:

- 21 CFR 211.176: Penicillin contamination
- [FDA Guide to Inspections: Validation of Cleaning Processes](#)

Date: 6/17/2015

12. Is there an acceptable level of penicillin residue in non-penicillin drug products?

No. There is no established safe level of penicillin residue in non-penicillin drug products (see FDA guidance for industry, referenced below). The CGMP regulations in 21 CFR 211.42(d) and 211.46(d) require that penicillin-manufacturing facilities and air-handling systems must be adequately separated from those used to manufacture other drugs. 21 CFR 211.176 states that a non-penicillin drug product must not be marketed if penicillin is found when tested according to the codified procedure. Alternative validated test methods to detect penicillin residues may be used if demonstrated to be equivalent to or better than the referenced method.

References:

- 21 CFR 211.176: Penicillin contamination
- 21 CFR 211.42(d): Design and construction features
- 21 CFR 211.46(d): Ventilation, air filtration, air heating and cooling
- FDA Guidance for Industry, 2013, Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing cross contamination
- [FDA BY-Lines No. 8, Nov 1977, A Review of Procedures for the Detection of Residual Penicillins in Drugs](#)

Date: 6/17/2015

13. For injectable drugs in multiple-dose containers, is the number of entries to withdraw a dose a factor in determining the expiration date? Generally, no. Unless the multiple-dose container is labeled to yield a specific number of doses of a stated volume, there is no limit to the number of withdrawals that may be made from a multiple-dose container before the drug

is depleted or reaches its expiration date. The primary concern with multiple-dose containers is the potential for contaminating the product during multiple penetrations through the container stopper. Although the expiration date assigned to such products would be based on the stability of the drug product, stability protocols should include requirements for testing and evaluating container-closure integrity. Container-closure integrity testing may include physically testing the closure seal by using a leak test and monitoring the system's ability to prevent microbial contamination. For multiple-dose injection product containers, functionality testing can include a self-sealing capacity test involving multiple penetrations of a hypodermic needle through the container stopper (see USP references below). Furthermore, injectable drug products in multiple-dose containers are generally formulated with an antimicrobial agent or preservative—or they contain inherently antimicrobial ingredients—and must meet requirements in accordance with the approved application (new drug application/abbreviated new drug application, biologics license application) and/or USP requirements.

References:

- 21 CFR 211.166: Stability testing
- USP 38–NF 33 (2015) General Chapter <1> Injections
- USP 38–NF 33 (2015) General Chapter <381> Elastomeric Closures for Injections
- FDA Guidance for Industry, 1996, ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
- FDA Guidance for Industry, 2003, ICH Q1A(R2) Stability Testing of New Drug Substances and Products
- FDA Guidance for Industry, 1996, ICH Q1C Stability Testing for New Dosage Forms
- FDA Guidance for Industry, 2013, ANDAs: Stability Testing of Drug Substances and Products
- FDA Guidance for Industry, 2014, ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers
- FDA Guidance for Industry, 2008, Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products

Date: 6/17/2015

14. How long may a firm store in-process/intermediate powder blends and triturations, sustained-release pellets/beads, and tablet cores, absent separate stability studies, before using them in finished drug products? For in-process/intermediate materials that are chemically and physically stable, a risk- and science-based assessment process can help identify which material attributes and process parameters might affect the critical quality attributes of the finished drug product in which they are to be used. This assessment should be designed to ensure that materials held (under appropriate storage conditions) for a specified period are appropriate for use in manufacturing the finished drug product without having to conduct formal stability studies to verify the holding periods. In some instances, the risk assessment may include sampling and testing the material being held (at the stage determined by the risk assessment) to verify the manufacturing holding period. However, for unstable materials or for materials held longer than the period established in the risk assessment, firms should conduct stability studies according to an approved stability protocol to verify holding periods. The stability studies should include evaluations of the in-process/intermediate materials up to the time of their use in manufacturing a finished drug product and should include long-term monitoring of finished product batches manufactured with the in-process/intermediate materials. In the latter case, until appropriate stability data are generated, firms should calculate the expiration date assigned to finished product batches based on the date of manufacture/release of the in-process/intermediate material rather than on that of the finished product.

References:

- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- 21 CFR 211.111: Time limitations on production

Date: 6/17/2015

15. What material can be used as instrument calibration standards for chromatographic systems? For chromatographic systems, instrument calibration standards should be chosen from highly purified materials that are well characterized and can be accurately weighed. Standards can be compendial (from USP) or non-compendial (e.g., from NIST, a chemical supplier, or produced in-

house). Substances obtained from a chemical supplier or produced in-house should be purified and characterized using validated purification processes and validated characterization methods. Purification is necessary because impurities can add variation and interfere with analytical methods. Finished dosage forms generally should be avoided as standards because excipients in the finished dosage form may interfere with analysis.

References:

- FDA guidance for industry, 2015, Analytical Procedures and Methods Validation for Drugs and Biologics
- 21 CFR 211.160(b)(4): Instrument calibration
- 21 CFR 211.194(a)(2) and (c): Method validation and reference standards
- USP General Chapter <621> *Chromatography*, section on System Suitability

Date: 8/12/2019

16. What material can be used for system suitability? FDA expects system suitability to be checked using qualified primary or secondary reference standards and any materials necessary to ensure adequate method performance. A new batch of highly pure reference standard material (e.g., from a chemical supplier or produced in-house) should be qualified against the primary reference standard. Finished dosage forms or APIs that have not been qualified as reference standards should not be used for system suitability testing. Even when API or a finished dosage form has been properly qualified as a reference standard, it should not be used for system suitability testing if it is from the same batch as sample(s) being tested. Written procedures must be established and followed (21 CFR 211.160 and 211.194). All data — including obvious errors and failing, passing, and suspect data — must be in the CGMP records and subject to review and oversight. Records must be complete (e.g., 21 CFR 211.68(b), 211.188, and 211.194) and subjected to adequate review (21 CFR 211.68(b), 211.186(a), 211.192, and 211.194(a)(8)).

References:

- FDA guidance for industry, 2015, Analytical Procedures and Methods Validation for Drugs and Biologics
- FDA guidance for industry, 2018, Data Integrity and Compliance With Drug CGMP: Questions and Answers
- USP General Chapter <621> *Chromatography*, section on System Suitability

Date: 8/12/2019

17. Is it ever appropriate to perform a “trial injection” of samples? No. FDA has observed at some drug manufacturers the practice of a trial injection where a sample of a lot is injected into the chromatographic system with the intention of obtaining an unofficial result (e.g., passing or failing). This is in contrast to the appropriate practice where an injection of a standard is performed with the sole intention of determining if the chromatographic system is fit for purpose. The injection of trial samples is not acceptable, in part, because all data from analysis of product samples must be retained and reviewed (21 CFR 211.22, 211.165, 211.192, and 211.194). Furthermore, uncertainty about system performance may also suggest a potential insufficiency of the method’s design, validation status, analyst training, equipment maintenance, or other fundamental problem(s) in the laboratory that should be promptly corrected.

Column conditioning does not involve injecting a sample from a lot and is not considered a trial injection. When its use is scientifically justified, column conditioning should be fully described in the method validation package as to the conditions needed to make the measurement (i.e., based on data from the method validation) and should be clearly defined in an approved and appropriate procedure. Only validated test methods that demonstrate accuracy, sensitivity, specificity, and reproducibility may be used to test drugs (21 CFR 211.165(e)). Consistent and unambiguous injection nomenclature should be used, and all data from the column conditioning, including audit trail data, should be maintained and subject to review.

Therefore, FDA considers it a violative practice to perform a trial injection (including under the guise of column conditioning). FDA also considers it a violative practice to use an actual sample in *test*, *prep*, or *equilibration* runs as a means of disguising testing into compliance.

References:

- FDA guidance for industry, 2015, Analytical Procedures and Methods Validation for Drugs and Biologics
- 21 CFR 211.194(a)(2): Method validation

Date: 8/12/2019

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4.8. Records and Reports

1. Some products, such as transdermal patches, are made using manufacturing processes with higher in-process material reject rates than for other products and processes. Is this okay?

Maybe. It depends on the cause and consistency of the reject rate. Many transdermal patch manufacturing processes produce more waste (i.e., lower yield from theoretical) than other pharmaceutical processes. This should not of itself be a concern. The waste is usually due to the cumulative effect of roll splicing, line start-ups and stoppages, roll-stock changes, and perhaps higher rates of in-process sampling. This is most pronounced for processes involving lamination of rolls of various component layers. Roll-stock defects detected during adhesive coating of the roll, for example, can often only be rejected from the roll after final fabrication/lamination of the entire patch, which contributes to the final process waste stream.

We expect that validated and well-controlled processes will achieve fairly consistent waste amounts batch-to-batch. Waste in excess of the normal operating rates may need (see 21 CFR 211.192) to be evaluated to determine cause (e.g., due to increase in sampling or higher than normal component defects ... or both) and the consequences on product quality assessed. We've seen a small number of cases where unusually high intra-batch rejects/losses were due to excessive component quality variability and poorly developed processes.

References:

- 21 CFR 211.100: Written procedures; deviations
- 21 CFR 211.103: Calculation of yield
- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- 21 CFR 211.192: Production record review

2. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?

The CGMP regulations (21 CFR parts 210 and 211) for finished pharmaceutical manufacturing do not specifically address the requirement to conduct, or to keep records of, internal quality assurance audits. If the report in question was from a routine audit to verify that the firm's quality system is operating as intended, then it would be acceptable if the firm elected to discard the report once all corrections have been verified.

However, any documentation of corrective action as a result of such an audit would have to be retained (see §§ 211.180 and 211.188). For example, if a routine internal audit finds a problem with a mixing step and the outcome is a change in mixing time, all affected procedures, including the master production record, are to reflect the necessary changes, and such records are subject to FDA inspection as usual. Any investigation into the impact this problem had on related batches is to be retained and also made available for inspection by FDA (see § 211.192).

In addition, any reports of investigations or evaluations prepared in response to, for example, a product complaint (§ 211.198), vendor qualification (§ 211.84), periodic review of records and data (§ 211.180(e)), and a failure investigation (§ 211.192) are not internal audits as discussed above. Such records are subject to FDA inspection and must be retained for at least the time specified in the CGMP regulations (see § 211.180).

References:

- 21 CFR 211.84: Testing and approval/rejection of components, drug product containers, and closures
- 21 CFR 211.180: General requirements
- 21 CFR 211.188: Batch production and control records
- 21 CFR 211.192: Production record review
- 21 CFR 211.198: Complaint files
- [Preamble to the Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding](#) regulations (43 FR 45015, paragraph 4, Sept 29, 1978)
- Compliance Policy Guide Sec. 130.300 [FDA Access to Results of Quality Assurance Program Audits and Inspections](#) (CPG 7151.02)

3. How do the part 11 regulations and "predicate rule requirements" (in 21 CFR part 211) apply to the electronic records created by computerized laboratory systems and the associated printed chromatograms that are used in drug manufacturing and testing?

Some in industry misinterpret the following text from the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (*Part 11* guidance, lines 164-171) to mean that in all cases paper printouts of electronic records satisfy predicate rule requirements in 21 CFR part 211:

Under the narrow interpretation of the scope of part 11, with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be 'using electronic records in lieu of paper records' under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11.

The *Part 11* guidance also states (in lines 150-152) that:

Persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules.

For high performance liquid chromatography (HPLC) and gas chromatography (GC) systems (and other computerized systems involving user inputs, outputs, audit trails, etc.), the predicate rules, such as 21 CFR 211.68 and 211.180(d), require the electronic records themselves to be retained and maintained in accordance with those regulations. Section 211.180(d) requires records to be retained "either as original records or true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records." Section 211.68 further states that: "[H]ard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are *exact and complete* and that it is secure from alteration, inadvertent erasures, or loss shall be maintained" (emphasis added). The printed paper copy of the chromatogram would not be considered a *true copy* of the entire electronic raw data used to create that chromatogram, as required by § 211.180(d). The printed chromatogram would also not be considered an *exact and complete* copy of the electronic raw data used to create the chromatogram, as required by § 211.68. The chromatogram does not generally include, for example, the injection sequence, instrument method, integration method, or the audit trail, of which all were used to create the chromatogram or are associated with its validity. Therefore, the printed chromatograms used in drug manufacturing and testing do not satisfy the predicate rule requirements in part 211. The electronic records created by the computerized laboratory systems must be maintained under these requirements.

We recognize that there are cases where it could be appropriate for the printed chromatogram to be used within laboratories for the review of test results. Similarly, it also may be acceptable to provide the printed chromatogram during a regulatory inspection or for application review purposes. However, the electronic record must be maintained and readily available for review by, for example, quality control/quality assurance personnel or the FDA investigator.

In summary, decisions on how to maintain records for computerized systems should be based on predicate rule requirements. We recommend that these decisions be supported by a sound risk assessment.

References:

- FDA Guidance for Industry, 2003, [Part 11, Electronic Records; Electronic Signatures—Scope and Application](#)
- 21 CFR 211.180(d): General requirements
- 21 CFR 211.68: Automatic, mechanical, and electronic equipment

Date: 8/3/2010

4. How does the FDA interpret the regulations (21 CFR part 211) regarding the establishment of expiry dating for chemicals, reagents, solutions, and solvents?

Laboratory "reagents, and standard solutions," as referenced in the CGMP regulations at 21 CFR 211.194, includes laboratory chemicals such as solvents (including mobile phases), dry chemicals (salts, primary standards, etc.), and solutions (buffers, acids/bases, quantitative analytical preparations, etc.), whether purchased or prepared in-house. Laboratory reagents and solutions are used in analytical tests of components, in-process materials, and finished products.

If the purchased laboratory reagent or solution includes a manufacturer's suggested use-by or expiry date, that date should be followed. For purchased laboratory reagents and solutions without a "use by" or expiry date, FDA would expect that an assessment be conducted (a literature review may be acceptable) of that specific chemical's or chemical family's stability and that an appropriate use-by or expiry date be determined.

For in-house prepared solutions, such as mobile phases or other nonquantitative solutions, FDA would expect that an assessment be conducted (again, literature review may be acceptable) to determine an appropriate expiry period. However, for in-house prepared solutions used for quantitative analysis, such as sample or standard solutions used in assay or impurity testing or titration solutions, FDA requires that formal stability studies be conducted to determine an appropriate expiry. As mentioned in the ICH guidance for industry *Q2B Validation of Analytical Procedures: Methodology*, the stability of analytical solutions is a typical method variation that should be evaluated during robustness testing during method validation. Method validation is a CGMP requirement at 21 CFR 211.160(b).

The determined use-by or expiry dates should be documented within a procedure and followed. Procedures for any in-house prepared laboratory solution should include the determined stability timeframe and should instruct that these solutions be labeled with the appropriately determined use-by or expiry date upon preparation and discarded upon expiration.

These principles would also apply to active pharmaceutical ingredient (API) manufacturing and testing sites. The use of "reagents and solutions" and use-by dates are found throughout the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*.

References:

- CFR 211.160: [General requirements](#)
- CFR 211.194: [Laboratory records](#)
- FDA Guidance for Industry, 2001, [ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients](#), Section 11, Laboratory Controls
- FDA Guidance for Industry, 1996, [ICH Q2B Validation of Analytical Procedures: Methodology](#)

Date: 7/19/2011

Contact for further information:CDER-OPQ-Inquiries@fda.hhs.gov**4.9. Returned and Salvaged Drug Products****1. What should a firm do if its drug products or components have been subjected to improper storage conditions such as those caused by a natural disaster?**

Drug products that have been subjected to improper storage conditions (including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation) due, for example, to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Such exposure can pose a serious risk to a drug's identity, strength, quality, purity or

safety (see 21 CFR 211.208). This fundamental CGMP principle applies to any component, in-process material, or finished drug product subjected to such conditions. In some cases, there may be substantial and reasonable uncertainty whether a drug was subjected to these conditions. In such a circumstance, it is essential that a firm nonetheless err on the side of caution in its risk assessment to ensure an appropriate lot disposition decision and conduct a rigorous evaluation in accordance with the standards described under § 211.208. When there is reasonable uncertainty whether a drug was subjected to such conditions, salvaging operations may be conducted only if there is evidence from laboratory testing that the drugs meet all applicable standards of identity, strength, quality, and purity, and from inspection that the drugs and their associated packaging were not subject to improper storage conditions as a result of the disaster or accident. When determining whether drugs have been subjected to such improper conditions, a firm's actions should include but not be limited to:

- Obtaining supply chain information, including knowing the names and addresses of all suppliers and distributors of a drug (including components and packaging) to determine if there is a reasonable possibility that such materials were stored under improper conditions.
- Determining details such as the time frame, duration, nature, scope, and location of exposure as well as identity of all lots potentially subjected to the improper conditions (e.g., ramifications of a natural disaster such as power disruptions should be considered to ensure a complete risk assessment).
- Obtaining certification (either on the certificate of analysis or as a separate statement) declaring that drug lots, including components and packaging, were not subjected to improper storage conditions.

References:

- 21 CFR 211.208: [Drug product salvaging](#)

2. What if the improper storage conditions include exposure to toxic fumes or radiation?

Exposure to potentially harmful levels of toxic fumes or radiation is considered to be an improper storage condition (see above). It is essential that firms exercise due diligence to ensure that their drugs were manufactured, processed, packaged, and held under conditions consistent with CGMP. This includes ensuring acceptability of both raw materials and drug products. FDA routinely monitors the quality of marketed drug products, including those imported into the United States. In response to natural disasters, FDA may increase its monitoring and detection capabilities and apply appropriate regulatory action to help ensure the quality and safety of the drug supply.

References:

1. FDA Import Alert 99-33, 2015, [Detention Without Physical Examination of Products from Japan Due to Radionuclide Contamination](#)
2. FDA Public Health Focus, [FDA Response to the Fukushima Dai-ichi Nuclear Power Facility Incident](#)
3. European Commission, 2011, [Food Safety: The EU Reinforces Controls on Imports from Japan](#)

3. What should be considered in performing an assessment of whether a firm's drug product, or its components or packaging materials, may have been contaminated with radioactive material?

Radioactive materials (radionuclides) release radiation, also called ionizing radiation, as high-energy particles or electromagnetic energy (e.g., gamma rays) as their unstable atoms transition to a more stable state. Low levels of radiation occur naturally in the environment (as background radiation), but elevated levels may occur, for example, during or following a nuclear reactor accident. Radioactive materials released into the environment by such an accident may contaminate drug products, components, or packaging materials. In these circumstances, firms should determine if any of these articles has become contaminated with radionuclides. If a drug product has been subjected to improper storage, including contamination with radioactive material, the product must not be salvaged and returned to the marketplace (21 CFR 211.208). Similarly, contaminated drug components and packaging materials should not be used or salvaged to manufacture drug products. It is important for manufacturers to know the origin and complete supply chain of a drug product, component, or

packaging to better enable an assessment for possible contamination arising from, for example, the accidental release of radioactivity.

Some general concerns about radionuclide contamination from nuclear accidents include, but are not limited to, the following:

- Drug products and/or components may become contaminated with radionuclides from various sources, including contaminated atmospheric fallout, ground water, soil, or naturally derived raw materials.
- A contaminated water supply used in drug manufacture may result in poor-quality products that fail to meet specifications.
- Certain dosage forms, such as injectable and inhalable drugs, may present greater risk to patients if contaminated with radionuclides, because these drugs more directly enter into the bloodstream.
- Drug products and/or drug components contaminated with radionuclides may result in poor-quality products that fail to meet stability specifications (e.g., reduced efficacy).

Manufacturers of finished drugs must ensure that their products comply with FDA regulations, which includes assurance that the components are of appropriate quality (see, e.g., 21 CFR part 211). In addition, manufacturers of drug components and primary containers must also ensure the quality of their material. FDA expects drug manufacturers and distributors to be extra vigilant and to take enhanced measures to ensure the quality and safety of their drugs that may have been exposed to radioactive contaminants. It may be appropriate for a firm to undertake measures to prevent purchase of at-risk materials as well as to increase testing of incoming components and finished products before final release. See 21 CFR part 211, including:

21 CFR 211.65, Testing and release for distribution

21 CFR 211.84, Testing and approval or rejection of components, drug product containers, and closures

21 CFR 211.94, Drug product containers and closures

21 CFR 211.208, Drug product salvaging

References:

21 CFR part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals

FDA Import Alert 99-33, 2015, Detention Without Physical Examination of Products from Japan Due to Radionuclide Contamination

FDA Public Health Focus, FDA Response to the Fukushima Dai-ichi Nuclear Power Facility Incident

Date updated June 18, 2015

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4.10 Data Integrity and Compliance With Drug CGMP

QUESTIONS AND ANSWERS

1. Please clarify the following terms as they relate to CGMP records:

a. What is "data integrity"?

For the purposes of this guidance, *data integrity* refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).⁵

Data integrity is critical throughout the CGMP data life cycle, including in the creation, modification, processing, maintenance, archival, retrieval, transmission, and disposition of data after the record's retention period ends.⁶ System design and controls should enable easy detection of errors, omissions, and aberrant results throughout the data's life cycle.

b. What is "metadata"?

Metadata is the contextual information required to understand data. A data value is by itself meaningless without additional information about the data. Metadata is often described as data about data. Metadata is structured information that describes, explains, or otherwise makes it easier to retrieve, use, or manage data. For example, the number "23" is meaningless without metadata, such as an indication of the unit "mg." Among other things, metadata for a particular piece of data could include a date/time stamp documenting when the data were acquired, a user ID of the person who conducted the test or analysis that generated the data, the instrument ID used to acquire the data, material status data, the material identification number, and audit trails.

Data should be maintained throughout the record's retention period with all associated metadata required to reconstruct the CGMP activity (e.g., §§ 211.188 and 211.194). The relationships between data and their metadata should be preserved in a secure and traceable manner.

c. What is an "audit trail"?

For purposes of this guidance, *audit trail* means a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record. For example, the audit trail for a high performance liquid chromatography (HPLC) run should include the user name, date/time of the run, the integration parameters used, and details of a reprocessing, if any. Documentation should include change justification for the reprocessing.

Audit trails include those that track creation, modification, or deletion of data (such as processing parameters and results) and those that track actions at the record or system level (such as attempts to access the system or rename or delete a file).

CGMP-compliant record-keeping practices prevent data from being lost or obscured and ensure that activities are documented at the time of performance (see §§ 211.68, 211.100, 211.160(a), 211.188, and 211.194). Electronic record-keeping systems, which include audit trails, can support these CGMP requirements.

⁵ These characteristics are important to ensuring data integrity and are addressed throughout the CGMP regulations for drugs. For *attributable*, see §§ 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10); for *legible*, see §§ 211.180(e) and 212.110(b); for *contemporaneously recorded* (at the time of performance), see §§ 211.100(b) and 211.160(a); for *original or a true copy*, see §§ 211.180 and 211.194(a); and for *accurate*, see §§ 211.22(a), 211.68, 211.188, and 212.60(g).

⁶ For examples of record retention periods, see §§ 211.180 and 212.110(c).

d. How does FDA use the terms "static" and "dynamic" as they relate to record formats?

For the purposes of this guidance, *static* is used to indicate a fixed-data record such as a paper record or an electronic image, and *dynamic* means that the record format allows interaction between the user and the record content. For example, a dynamic chromatographic record may allow the user to change the baseline and reprocess chromatographic data so that the resulting peaks may appear smaller or larger. It also may allow the user to modify formulas or entries in a spreadsheet used to compute test results or other information such as calculated yield.

e. How does FDA use the term "backup" in § 211.68(b)?

FDA uses the term *backup* in § 211.68(b) to refer to a true copy of the original record that is maintained securely throughout the record retention period (e.g., § 211.180). Backup data must be exact, complete, and secure from alteration, inadvertent erasures, or loss (§ 211.68(b)). The backup file should contain the data (which includes associated metadata) and should be in the original format or in a format compatible with the original format.

FDA's use of the term *backup* is consistent with the term *archive* as used in guidance for industry and FDA staff *General Principles of Software Validation*.

Temporary backup copies (e.g., in case of a computer crash or other interruption) would not satisfy the requirement in § 211.68(b) to maintain a backup file of data.

f. What are the "systems" in "computer or related systems" in § 211.68?

The American National Standards Institute (ANSI) defines systems as people, machines, and methods organized to accomplish a set of specific functions.⁷ *Computer or related systems* can refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, personnel, and associated documents (e.g., user manuals and standard operating procedures).⁸

2. When is it permissible to invalidate a CGMP result and exclude it from the determination of batch conformance?

Data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria (see §§ 211.22 and 212.70) and maintained for CGMP purposes (e.g., § 211.180).⁹ Electronic data generated to fulfill CGMP requirements include relevant metadata required to reconstruct the CGMP activity captured in the record. Invalidating test results to exclude them from quality unit decisions about conformance to a specification requires a valid, documented, scientifically sound justification. See, for example, §§ 211.160(b), 211.188, 211.192, and 212.71(b) and the guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*. Even if test results are legitimately invalidated on the basis of a scientifically sound investigation, the full CGMP batch record provided to the quality unit would include the original (invalidated) data, along with the investigation report that justifies invalidating the result. The requirements for record retention and review do not differ depending on the data format; paper-based and electronic data record-keeping systems are subject to the same requirements.

⁷ American National Standard for Information Systems, *Dictionary for Information Systems*, American National Standards Institute, 1991.

⁸ See guidance for industry and FDA staff *General Principles of Software Validation*.

⁹ For purposes of this guidance, the term *quality unit* is synonymous with the term *quality control unit*. For the definition of *quality control unit*, see § 210.3(b)(15).

3. Does each CGMP workflow on a computer system need to be validated?

Yes, a CGMP workflow, such as creation of an electronic master production and control record (MPCR), is an intended use of a computer system to be checked through validation (see §§ 211.63, 211.68(b), and 211.110(a)). The extent of validation studies should be commensurate with the risk posed by the automated system. When the same system is used to perform both CGMP and non-CGMP functions, the potential for non-CGMP functions to affect CGMP operations should be assessed and mitigated appropriately.¹⁰

If you validate the computer system but you do not validate it for its intended use, you cannot know if your workflow runs correctly.¹¹ For example, qualifying the Manufacturing Execution System (MES) platform, a computer system, ensures that it meets its relevant requirements and specifications; however, it does not demonstrate that a given MPCR generated by the MES contains the correct calculations. In this example, validating the workflow ensures that the intended steps, requirements, and calculations in the MPCR are accurate and perform properly. This is similar to reviewing a paper MPCR and ensuring all supporting procedures are in place before the MPCR is implemented in production (see §§ 211.100, 211.186, and 212.50(b) and the guidance for industry *PET Drugs—Current Good Manufacturing Practice (CGMP)*).

FDA recommends you implement appropriate controls to manage risks associated with each element of the system. Controls that are appropriately designed to validate a system for its intended use address software, hardware, personnel, and documentation.

4. How should access to CGMP computer systems be restricted?

You must exercise appropriate controls to assure that changes to computerized MPCRs or other CGMP records or input of laboratory data into computerized records can be made only by authorized personnel (§ 211.68(b)). Other examples of records for which control should be restricted to authorized personnel include automated visual inspection records, electronic materials management system records, and automated dispensing system weighing records. FDA recommends that you restrict the ability to alter specifications, process parameters, data, or manufacturing or testing methods by technical means where possible (e.g., by limiting permissions to change settings or data).

The system administrator role, including any rights to alter files and settings, should be assigned to personnel independent from those responsible for the record content. To assist in controlling access, it is important that manufacturers establish and implement a method for documenting authorized personnel's access privileges for each CGMP computer system in use (e.g., by maintaining a list of authorized individuals) (see § 211.68(b)).

5. Why is FDA concerned with the use of shared login accounts for computer systems?

When login credentials are shared, a unique individual cannot be identified through the login and the system would not conform to the CGMP requirements in parts 211 and 212. FDA requires that system controls, including documentation controls, be designed in accordance with CGMP to assure product quality (e.g., §§ 211.100 and 212.50). For example, you must implement documentation controls that ensure that the actions as described in question 4 are attributable to a specific individual (see §§ 211.68(b), 211.188(b)(11), 211.194(a)(7) and (8), and 212.50(c)(10)).

Shared, read-only user accounts that do not allow the user to modify data or settings are acceptable for viewing data, but they do not conform with the part 211 and 212 requirements for actions, such as second person review, to be attributable to a specific individual.

¹⁰ See note 8.

¹¹ In computer science, *validation* refers to ensuring that software meets its requirements. However, this may not meet the definition of *process validation* as found in guidance for industry *Process Validation: General Principles and Practices*: "The collection and evaluation of data ... which establishes scientific evidence that a process is capable of consistently delivering quality products." See also ICH guidance for industry *Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*, which defines *validation* as providing assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. For purposes of this guidance, *validation* is being used in a manner consistent with the above guidance documents.

6. How should blank forms be controlled?

There must be document controls in place to assure product quality (see §§ 211.100, 211.160(a), 211.186, 212.20(d), and 212.60(g)). For example, bound paginated notebooks, stamped for official use by a document control group, provide good document control because they allow easy detection of unofficial notebooks as well as any gaps in notebook pages. If used, blank forms (e.g., electronic worksheets, laboratory notebooks, and MPCRs) should be controlled by the quality unit or by another document control method. As appropriate, numbered sets of blank forms may be issued and should be reconciled upon completion of all issued forms. Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement (see, e.g., §§ 211.192, 211.194, 212.50(a), and 212.70(f)(1)(vi)). All data required to recreate a CGMP activity should be maintained as part of the complete record.

7. Who should review audit trails?

Audit trail review is similar to assessing cross-outs on paper when reviewing data. Personnel responsible for record review under CGMP should review the audit trails that capture changes to data associated with the record as they review the rest of the record (e.g., §§ 211.22(a), 211.101(c) and (d), 211.103, 211.182, 211.186(a), 211.192, 211.194(a)(8), and 212.20(d)). For example, all production and control records, which includes audit trails, must be reviewed and approved by the quality unit (§ 211.192). The regulations provide flexibility to have some activities reviewed by a person directly supervising or checking information (e.g., § 211.188). FDA recommends a quality system approach to implementing oversight and review of CGMP records.¹²

8. How often should audit trails be reviewed?

If the review frequency for the data is specified in CGMP regulations, adhere to that frequency for the audit trail review. For example, § 211.188(b) requires review after each significant step in manufacture, processing, packing, or holding, and § 211.22 requires data review before batch release. In these cases, you would apply the same review frequency for the audit trail.

If the review frequency for the data is not specified in CGMP regulations, you should determine the review frequency for the audit trail using knowledge of your processes and risk assessment tools. The risk assessment should include evaluation of data criticality, control mechanisms, and impact on product quality.¹³

Your approach to audit trail review and the frequency with which you conduct it should ensure that CGMP requirements are met, appropriate controls are implemented, and the reliability of the review is proven.

See the audit trail definition in 1.c. above for further information on audit trails.

9. Can electronic copies be used as accurate reproductions of paper or electronic records?

Yes. Electronic copies can be used as true copies of paper or electronic records, provided the copies preserve the content and meaning of the original record, which includes all metadata required to reconstruct the CGMP activity and the static or dynamic nature of the original records.

True copies of dynamic electronic records may be made and maintained in the format of the original records or in a format that allows for the content and meaning of the original records to be preserved if a suitable reader and copying equipment (e.g., software and hardware, including media readers) are readily available (§§ 211.180(d) and 212.110).

¹² See guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations*. See also guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* for information about auditing as it relates to contract facilities.

¹³ Risks to data include, but are not limited to, the potential to be deleted, amended, or excluded without authorization or without detection. Examples of audit trails that may be appropriate to review on a risk-based frequency include audit trails that capture instrument operational status, instrument communication logs, and alert records.

10. Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument?

A paper printout or static record may satisfy retention requirements if it is the original record or a true copy of the original record (see §§ 211.68(b), 211.188, 211.194, and 212.60). During data acquisition, for example, pH meters and balances may create a paper printout or static record as the original record. In this case, the paper printout or static record, or a true copy, must be retained (§ 211.180).

However, electronic records from certain types of laboratory instruments—whether stand-alone or networked—are dynamic, and a printout or a static record does not preserve the dynamic record format that is part of the complete original record. For example, the spectral file created by FT-IR (Fourier transform infrared spectroscopy) is dynamic and can be reprocessed. However, a static record or printout is fixed and would not satisfy CGMP requirements to retain original records or true copies (§ 211.180(d)). Also, if the full spectrum is not displayed in the printout, contaminants may be excluded.

You must ensure that original laboratory records, including paper and electronic records, are subject to second-person review (§ 211.194(a)(8)) to make certain that all test results and associated information are appropriately reported. Similarly, in microbiology, a contemporaneous written record is maintained of the colony counts of a petri dish, and the record is then subject to second-person review.

Document control requirements in § 211.180 pertain only to CGMP records.

For more information on static and dynamic records, see 1.d. in this guidance. For PET drugs, see the guidance for industry *PET Drugs—Current Good Manufacturing Practice (CGMP)* for discussion of equipment and laboratory controls, including regulatory requirements for records.

11. Can electronic signatures be used instead of handwritten signatures for master production and control records?

Yes, electronic signatures with the appropriate controls can be used instead of handwritten signatures or initials in any CGMP required record. Although § 211.186(a) specifies a “full signature, handwritten,” an electronic signature with the appropriate controls to securely link the signature with the associated record fulfills this requirement (21 CFR 11.2(a)). See part 11, which establishes criteria for when electronic signatures are considered the legally binding equivalent of handwritten signatures. Firms using electronic signatures should document the controls used to ensure that they are able to identify the specific person who signed the records electronically.

There is no requirement for a handwritten signature for the MPCR in the PET CGMP regulations (21 CFR part 212).

12. When does electronic data become a CGMP record?

When generated to satisfy a CGMP requirement, all data become a CGMP record.¹⁴ You must document, or save, the data at the time of performance to create a record in compliance with CGMP requirements, including, but not limited to, §§ 211.100(b) and 211.160(a).

FDA expects processes to be designed so that data required to be created and maintained cannot be modified without a record of the modification. For example, chromatographic data should be saved to durable media upon completion of each step or injection (e.g., peak integration or processing steps; finished, incomplete, or aborted injections) instead of at the end of an injection set, and changes to the chromatographic data or injection sequence should be documented in an audit trail. Aborted or incomplete injections should be captured in audit trails and should be investigated and justified.

¹⁴ Under section 704(a) of the FD&C Act, FDA inspections of manufacturing facilities “shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs [and] nonprescription drugs intended for human use ... are adulterated or misbranded ... or otherwise bearing on violation of this chapter.” Accordingly, FDA routinely requests and reviews records not intended to satisfy a CGMP requirement but which nonetheless contain CGMP information (e.g., shipping or other records that may be used to reconstruct an activity).

It is not acceptable to record data on pieces of paper that will be discarded after the data are transcribed to a permanent laboratory notebook (see §§ 211.100(b), 211.160(a), and 211.180(d)). Similarly, it is not acceptable to store electronic records in a manner that allows for manipulation without creating a permanent record.

You may employ a combination of technical and procedural controls to meet CGMP documentation practices for electronic systems. For example, a computer system, such as a Laboratory Information Management System (LIMS) or an Electronic Batch Record (EBR) system, can be designed to automatically save after each entry. This would be similar to indelibly recording each entry contemporaneously on a paper batch record to satisfy CGMP requirements. The computer system described above could be combined with a procedure requiring data be keyed in or otherwise entered immediately when generated.

For PET drugs, see the “Laboratory Controls” section of the guidance for industry *PET Drugs—Current Good Manufacturing Practice (CGMP)*.

13. Why has FDA cited use of actual samples during “system suitability” or test, prep, or equilibration runs in warning letters?

FDA prohibits sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result (e.g., testing different samples until the desired passing result is obtained). This practice, also referred to as *testing into compliance*, is not consistent with CGMP (see the guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*). In some situations, use of actual samples to perform system suitability testing has been used as a means of testing into compliance. FDA considers it a violative practice to use an actual sample in *test, prep, or equilibration* runs as a means of disguising testing into compliance.

According to the United States Pharmacopeia (USP), system suitability tests must include replicate injections of a standard preparation or other standard solutions to determine if requirements for precision are satisfied (see USP General Chapter <621> *Chromatography*). System suitability tests should be performed according to the firm’s established written procedures—which should include the identity of the preparation to be injected and the rationale for its selection—and the approved application or applicable compendial monograph (§§ 211.160 and 212.60).

If an actual sample is to be used for system suitability testing, it should be a properly characterized secondary standard, written procedures should be established and followed, and the sample should be from a different batch than the sample(s) being tested (§§ 211.160, 211.165, and 212.60). CGMP original records must be complete (e.g., §§ 211.68(b), 211.188, 211.194) and subjected to adequate review (§§ 211.68(b), 211.186(a), 211.192, and 211.194(a)(8)). Transparency is necessary. All data—including obvious errors and failing, passing, and suspect data—must be in the CGMP records that are retained and subject to review and oversight. An investigation with documented, scientifically sound justification is necessary for data to be invalidated and not used in determining conformance to specification for a batch (see §§ 211.160, 211.165, 211.188, and 211.192).

For more information, see the ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* and VICH guidances for industry *GL1 Validation of Analytical Procedures: Definition and Terminology* and *GL2 Validation of Analytical Procedures: Methodology*.¹⁵

14. Is it acceptable to only save the final results from reprocessed laboratory chromatography?

No. Analytical methods should be accurate and precise.¹⁶ For most lab analyses, reprocessing data should not be regularly needed. If chromatography is reprocessed, written procedures must be established and followed and each result retained for review (see §§ 211.160, 211.165(c), 211.194(a)(4), and 212.60(a)). FDA requires complete data in laboratory records, which includes but is not limited to notebooks, worksheets, graphs, charts, spectra, and other types of data from laboratory instruments (§§ 211.194(a) and 212.60(g)(3)).

¹⁵ VICH=Veterinary International Conference on Harmonisation.

¹⁶ See ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology*.

15. Can an internal tip or information regarding a quality issue, such as potential data falsification, be handled informally outside of the documented CGMP quality system?

No. Regardless of intent or how or from whom the information was received, suspected or known falsification or alteration of records required under parts 210, 211, and 212 must be fully investigated under the CGMP quality system to determine the effect of the event on patient safety, product quality, and data reliability; to determine the root cause; and to ensure the necessary corrective actions are taken (see §§ 211.22(a), 211.125(c), 211.192, 211.198, 211.204, and 212.100).

FDA invites individuals to report suspected data integrity issues that may affect the safety, identity, strength, quality, or purity of drug products at DrugInfo@fda.hhs.gov. "CGMP data integrity" should be included in the subject line of the email. This reporting method is not intended to supersede other FDA reports (e.g., field alert reports or biological product deviation reports that help identify drug products that pose potential safety threats).

16. Should personnel be trained in preventing and detecting data integrity issues as part of a routine CGMP training program?

Yes. Training personnel to prevent and detect data integrity issues is consistent with the personnel requirements under §§ 211.25 and 212.10, which state that personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties.

17. Is FDA allowed to look at electronic records?

Yes. All records required under CGMP are subject to FDA inspection. This applies to records generated and maintained on computerized systems, including electronic communications that support CGMP activities. For example, an email to authorize batch release is a CGMP record that FDA may review.

You must allow authorized inspection, review, and copying of records, which includes copying of electronic data (§§ 211.180(c) and 212.110(a) and (b)). See also the guidance for industry *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection* and section 704 of the FD&C Act. Procedures governing the review of electronic records are described in chapter 5 of the *Investigations Operations Manual (IOM)* at <https://www.fda.gov/iceci/inspections/iom/default.htm>.

18. How does FDA recommend data integrity problems be addressed?

FDA encourages you to demonstrate that you have effectively remediated your problems by investigating to determine the problem's scope and root causes, conducting a scientifically sound risk assessment of its potential effects (including impact on data used to support submissions to FDA), and implementing a management strategy, including a global corrective action plan that addresses the root causes. This may include retaining a third-party auditor and removing individuals responsible for data integrity lapses from positions where they can influence CGMP-related or drug application data at your firm. It also may include improvements in quality oversight, enhanced computer systems, and creation of mechanisms to prevent recurrences and address data integrity breaches (e.g., anonymous reporting system, data governance officials and guidelines).

These expectations mirror those developed for the Application Integrity Policy. For more detailed information, see *Points To Consider for Internal Reviews and Corrective Action Operating Plans* at <http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134744.htm>.

5. Health Canada

5.1 General Issues

Q.1 Are firms required to use high-efficiency particulate air (HEPA) filters for air supply in areas used for the manufacture of non-sterile dosage forms?

A.1 Division 2, Good Manufacturing Practices (GMP), of the *Food and Drug Regulations* does not specifically require manufacturing facilities for non-sterile drugs to maintain HEPA filtered air.

The Regulations do require the use of equipment for adequate control over air pressure, microorganisms, dust, humidity and temperature, when appropriate. In addition, this section calls for use of air filtration systems, including prefilters and particulate matter air filters on air supplies to production areas, as appropriate. These provisions speak to measures to prevent cross contamination, and the key phrase is "when appropriate".

Despite the lack of an explicit GMP requirement, some firms may elect to use HEPA filtered air systems as part of their dust control procedures. For example, firms may perform dust containment assessments and decide that such filters are warranted to prevent cross contamination of highly potent drugs that, even in small quantities, could pose a significant health hazard when carried over into other products.

Q.2 Is there an acceptable substitute for dioctyl phthalate (DOP) to integrity testing of high-efficiency particulate air (HEPA) filters?

A.2 Yes. Dioctyl phthalate aerosols also called Di (2-ethylhexyl) phthalate, di-sec octyl phthalate, DOP, or DEHP, have long been used to test the integrity of HEPA filters but concern about the potential health effects to people working with DOP test aerosols has led to a search for a safer equivalent replacement.

The product of choice from US Army testing with assistance from various private companies was a Henkel Corporation (Emery Group) product called Emery 3004 PAO. This product is a polyalphaolefin (POA) in the 4 centistoke (4 cSt) viscosity grade, used primarily as a lubricant base stock for oils, lubricants, and electrical/hydraulic fluids.

Emery 3004 (POA) can replace DOP in HEPA integrity testing.

Q.3 What is the acceptable limit for dew point of the compressed air used in pneumatic equipment and to dry the manufacturing tanks after cleaning?

A.3 Under the "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)", there is no limit for the relative humidity % of the air used for pneumatic equipment and to dry manufacturing tanks. From a general perspective, based on Interpretation 4 under Section C.02.004 Premises, the humidity must be controlled where required to safeguard sensitive materials. Consequently, it is the fabricator, packager/labeller's responsibility to establish the pertinence of such control. If the humidity % of the compressed air used at the last step of drying of a reservoir is too high, micro-droplets of water could be generated on the internal surfaces by condensation, hence contributing to the possibility of microbial growth following storage. Similarly, it is important to make sure that residual water has been completely eliminated from hard to reach surfaces of the equipment after cleaning operations.

Q.4 What are the requirements applicable to Quality Control (QC) and engineering personnel who travel many times daily between self-contained facilities and the regular facilities?

A.4 Movement of personnel between self-contained and other facilities must be subject to procedures that will prevent cross contamination. This may include but is not limited to decontamination procedures such as showering and change of clothes.

Q.5 What should be the standard of compressed air used in the manufacture of a drug?

A.5 Air that comes into direct contact with primary contact surfaces and/or the product should be monitored to control the level of particulates, microbial contamination, and the absence of hydrocarbons. Limits used should take into consideration the stage of manufacture, product, etc. Additional tests might be required due to the nature of the product. Gas used in aseptic processes must be sterile and filters checked for integrity.

Q.6 Does the concept of self-contained facilities apply equally to research and development laboratories (susceptible to contain highly sensitizing, highly potent or potentially pathogenic material in the analytical scale) that may be in the same building as the manufacturing facilities, or is this concept limited to actual manufacturing operations?

A.6 It is the responsibility of the manufacturer to ensure that their premises and operations have been designed in such a manner that the risk of contamination between products is minimized. This would include research and development areas within facilities where marketed drug products are fabricated and packaged. Further guidance can be found under Interpretation 11, Section C.02.004 Premises of the "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)".

Equipment - C.02.005

Q. 1 Should equipment be labelled with calibration dates?

A.1 Major equipment should be identified with a distinctive number or code that is recorded in batch records. This identification requirement is intended to help document which pieces of equipment were used to make which batches of drug product.

Division 2, Good Manufacturing Practices (GMP), of the *Food and Drug Regulations* does not require that each piece of equipment bear status labelling as to its state of calibration or maintenance. However, equipment must be calibrated and/or maintained according to an established schedule, and records must be kept documenting such activities.

The regulations do not distinguish critical from non-critical equipment for calibration and maintenance purposes. However, the need for calibrating a given piece of equipment depends on its function. In general, equipment that measure materials warrant calibration. Equipment not requiring calibration/maintenance need not be tracked or included in the firm's calibration/maintenance program, but the firm must be able to support its decision to exclude a particular piece of equipment from the calibration/maintenance program.

During an inspection a firm should be able to document when a specific piece of equipment was last calibrated/maintained, the results or action, and when its next calibration/maintenance is scheduled. The absence of such documentation is considered a GMP deviation. While the absence of a calibration/maintenance tag is not objectionable, the presence of a calibration/maintenance tag alone should not be assumed to satisfy regulatory demands, and the supporting documentation should be audited. The firm should also be able to support its decision to not include a particular piece of equipment in the calibration/maintenance program.

Personnel - C.02.006

Q.1 Is a company required to notify the Inspectorate of a change in key personnel, such as the person in charge of Quality Control (QC) or manufacturing department?


A.1 No. However, it is the company's responsibility to make sure that the new person meets the requirements of Interpretation 1, 2, 3, or 4 under C.02.006 Personnel, depending on the activities performed.

Sanitation - C.02.007 & C.02.008

Q.1 Is fumigation a requirement under sanitation?

A.1 The written sanitation program should include procedures for pest control as well as precautions required to prevent contamination of a drug when fumigating agents are used.

Fumigation is not a requirement per se. Infestation should be monitored and controlled. Where fumigation is used, appropriate precautions should be taken.

Methods of sanitary control that satisfy the requirements of Sections 8 and 11 of the  *Food and Drugs Act* would be considered to be acceptable.

Q.2 What limits are acceptable on product residues regarding sanitation?

A.2 Guidance for the establishment of limits can be obtained from the "Cleaning Validation Guidelines (GUI-0028)".

Q.3 Are gowning rooms required even in pilot plant operations?

A.3 Even in a pilot plant consisting of a small laminar flow area where the apparatus for filter sterilization of solutions are set up, it is an unacceptable practice to gown in there. A change room should be available besides their sterile pilot plant production area.

Based on the assumption that the pilot plant will produce drugs for sale - including clinical studies - then the same principles and considerations that apply to full scale production operations must also be utilized in pilot plant facilities.

Q.4 What are considered as being acceptable limits for cross contamination when performing cleaning validation?

A.4 Guidance for the establishment of limits can be obtained from the "Cleaning Validation Guidelines (GUI-0028)".

Q.5 In terms of cleaning, what would be the frequency and type of cleaning for equipment and premises for successive manufacturing of batches of the same product? And for different strengths of the same product?

A.5 Interpretation 3.5 under Section C.02.007 Sanitation specifies that "a cleaning procedure requiring complete product removal may not be necessary between batches of the same drug". The frequency and type of cleaning for equipment and premises must address the length of time between consecutive lots with the ultimate goal that a particular lot won't be contaminated by the previous lot or the environment. It must also ensure that residual quantities of the previous lot won't impact on the quality of the following lot. Thus, a partial cleaning would be required between two lots of the same product, especially for forms such as liquids or suspensions, in order to prevent a few units at the beginning of a new lot from being filled with residual quantities from the previous lot that may be located in equipment such as hoses or pumps. A procedure should be established to ensure adequate removal of residual quantities from the previous lot and validation available for the maximum period of time between two successive lots in order to avoid problems such as microbial contamination, accumulation of residue, or degradation of product. The number of lots of the same product which could be manufactured before a complete/full cleaning should be determined.

Q.6 Clothing: Is it acceptable to have two levels of clothing in the non-sterile manufacturing areas, i.e., one level for operators with full gowning and coveralls and another level for QA auditors and visitors? What environmental monitoring data is required?

A.6 Yes. There are basic clothing requirements for any person entering the manufacturing areas, such as hair, mustache and beard covering, as well as protective garments. However, a firm may decide to apply more stringent requirements for operators, such as dedicated shoes and garments providing a higher level of protection. There are no specific environmental monitoring requirements for clothing worn in the non-sterile manufacturing areas.

Q.7 Can the sampling for the microbial monitoring of air in non-sterile areas where susceptible products are produced be conducted when there are no manufacturing packaging activities?

A.7 The sampling should occur during actual manufacturing or packaging in order to reflect the conditions to which the products being produced are really exposed. Monitoring between production runs is also advisable in order to detect potential problems before they arise.

Q.8 Must written procedures be available to prevent objectionable microorganisms in drug products not required to be sterile?

A.8 Yes. Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, should be established and followed. This means that even though a drug product is not sterile, a firm must follow written procedures that pro-actively prevent contamination and proliferation of microorganisms that are objectionable.

Q.9 Should individuals who are known carriers of communicable disease be allowed to work in production areas?

A.9 Under Section C.02.008 of the "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)", a person who is a carrier of a disease in a communicable form should not have access to any area where a drug is exposed. The likelihood of disease transmission by means of a drug product would depend on the nature of the disease and the type of work the employee carries out. It may be advisable to consult with a physician. Certain diseases could be transmitted through a drug product if proper hygiene procedures are not followed by an infected employee handling the product. However, an employee may also be a carrier of a communicable disease and not be aware of it. Therefore, in addition to strict personal hygiene procedures, systems should be in place to provide an effective barrier that would preclude contamination of the product. These procedures must be followed at all times by all employees. In the event that an employee is found to be a carrier of a communicable disease, the company is to contact Health Canada and perform a risk analysis to determine if there is any affected drug products.

Raw Material Testing - C.02.009 & C.02.010

Q.1 What are requirements of maintaining an impurity profile?

A.1 The United States Pharmacopoeia (USP) defines an impurity profile as "a description of the impurities present in a typical lot of drug substance produced by a given manufacturing process." (ref. USP <1086>). Each commercial lot should be comparable in purity to this standard release profile which is developed early on and maintained for each pharmaceutical chemical. We can also call this profile a "Reference Profile" because the quality control unit refers to it (1) when assessing the purity of each batch of active pharmaceutical ingredient (API), and (2) when evaluating the viability of proposed process changes.

For further information regarding the control of impurities, please consult Impurities in New Drug Substances - ICH Q3A (R) & Impurities in New Drug Products - ICH Q3B (R).

Q.2 Does every individual container of a raw material need to be sampled for identification (ID) purposes regardless of the number of containers of the same lot available or are composite samples acceptable provided they are obtained from a maximum of 10 containers?

A.2 For human drugs, according to Interpretation 6.1 under C.02.009 Raw Material Testing, each container of a lot of a raw material must be tested for the identity of its contents. Therefore, each container of all raw materials, including excipients and active pharmaceutical ingredients (API), must be opened and sampled. Then, 2 options are available:

1. To test every sample for ID using a discriminating method (it is not mandatory to perform all ID tests in the specifications, for example United States Pharmacopoeia (USP), but the test must be specific).
2. If the raw material can be tested for potency, the other option is to mix and pool individual samples taken from each containers in a composite sample but without exceeding 10 individual samples in a composite. A specific ID test is then performed on each composite **and**, in addition, a potency test is performed to assure the mass balance of the composite. (In such cases, an equal quantity of each individual sample in the composite must be weighed to ensure that the mass balance is representative.)

As an example, say 72 containers of the same lot of a raw material are received. Each and all containers must be opened and a sample taken from each container. After that, the first option is to test each sample for ID (which implies 72 ID tests). The second option is to combine equal quantities of those individual samples in a way that the number of samples in any composite does not exceed 10 and test those composites for ID and potency. In this case, the easiest way to combine those samples would be 8 composites of 9 individual samples. For a given composite, a potency result of 88.8 % or so would indicate that one of the containers does not contain the right material as each individual sample contributes 1/9 or 11.11% of the total mass of the composite (similarly a result of 77,7 % would indicate 2 containers with the wrong material). In such case, each container selected for this particular composite would have to be tested for ID to pinpoint the one (or more) containers with the wrong material.

However, the use of a composite sample to establish the ID of a raw material cannot be used when the potency limits are too wide or, similarly, when the precision of the assay method is not sufficient to properly establish the mass balance.

Q.3a An active pharmaceutical ingredient (API) can be used after the retest date assigned by the API fabricator if a re-analysis done immediately before use shows that it still meets its specifications. Can the new data generated be used by the drug fabricator to assign a longer retest date to future lots of this API obtained from the same fabricator?

A.3a No. The extension of the retest date originally assigned to the API should be supported by data generated through a formal stability protocol. This may require the filing of a notifiable change submission. Please refer to the appropriate review Directorate.

Q.3b What about inactive ingredients?

A.3b Normally, any inactive raw material should bear an expiry date. When an inactive raw material is received without an expiry date, the fabricator should assign either an expiry date or a re-test date based on stability data or other documented evidence that this raw material is not subject to chemical / physical modifications or is not susceptible to microbial contamination.

Q.4 With respect to the re-test date of the drug substances, we have the stability data of a drug substance for up to 24 months at real time stability condition. The re-test period is assigned up to 24 months. According to the "Evaluation of Stability Data - ICH Q1E" , 2.4.1.1(the proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data), the retest period can be

assigned up to 36 months. Can we assign the retest period up 36 months? If yes, does it require retesting of the active pharmaceutical ingredient (API) at 24 months?

A.4 Retest period and expiry date for APIs should be based on stability data. If an expiry date has been assigned to an API then its batches cannot be used after the expiry period. However, if a retest period has been assigned to the API, then after the retest period is over the API batch can be tested and used immediately (e.g., within one month of the testing). In the scenario presented above extrapolation of expiry date beyond 24 months should be based on stability data both at long-term and accelerated storage conditions. If the test results are satisfactory the retest period can be extended to a period not exceeding 36 months. Once the retest period of the API has been extended to 36 months, testing batches at the 24 months time point would be part of the ongoing stability protocol (it will not be considered *retest*). For further guidance on retest period and expiry period please consult [Stability Testing of New Drug Substances - ICH Q1 A \(R2\)](#) & [Evaluation of Stability Data - ICH Q1E](#).

Q.5 We are a subsidiary of a United States (US) corporation. This US corporation supplies us with active pharmaceutical ingredients (APIs) that are fully tested after receipt on its premises. Can the US site be certified for the purpose of testing exemptions for the Canadian site?

A.5 The US parent company cannot be considered the vendor. To be certified, the vendor must be the original source of the API. In this instance, the US company would be acting as a contract laboratory and should meet the requirements under Interpretation 6.10, Section C.02.015 Quality Control Department. When received by the Canadian site, a specific identity test must be performed and if for an API, the testing must be as per Interpretation 6.1, Section C.02.009 Raw Material Testing (i.e., each container sampled and tested). The above mentioned would be acceptable based on the fact that no repackaging is done by the US site (i.e., the materials must be supplied in their original containers with the original labels and Certificate of Analysis (C of A) as received from the vendor).

Q.6 What documentation does a laboratory have to have in place to be considered qualified to run a test method for raw materials (drug substances and excipients) in order to satisfy Health Canada Regulations?

A.6 Documentation should include a summary of the analytical method validation, an assessment of the results and comparison to the acceptance criteria, and a conclusion as to the acceptability of the data as they relate to the ability of the laboratory analysts to successfully perform the procedure in the particular laboratory.

Q.7 Is the sampling plan based on the $(\sqrt{n+1})$ acceptable for identifying the number of containers of raw material to be sampled?

A.7 Sampling plans and procedures must be statistically valid and should be based on scientifically sound sampling practices taking into account the risk associated with the acceptance of the defective product based on predetermined classification of defects, criticality of the material, and past quality history of the vendor. In some circumstances, such as for large number of containers, a sampling plan based on $(\sqrt{n+1})$ may be acceptable. However, a sampling plan based on $(\sqrt{n+1})$ may present a significant risk of accepting defective goods in certain circumstances, such as the sampling of a small number of containers. As with all sampling plans, documented justification must be available.

Q8. If we already test each batch of our finished product for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, is it required to test it also for the purified water?

A8. Yes, you are required to test the purified water for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It is the general expectation that raw material testing support finished product testing.

Q.9 Interpretation 6.1 under Section C.02.009 specifies that "...each container of a lot of a raw material is tested for the identity of its contents using a specifically discriminating identity test." Does this requirement apply to raw materials used to fabricate finished products imported from non-Mutual Recognition Agreement (non-MRA) countries?

A.9 Any drug that is imported into Canada must meet the requirements in Division 2, Part C of the [Food and Drug Regulations](#). The sampling and testing requirements for raw materials used in finished products imported from non-MRA countries should be equivalent to the requirements in Division 2, Part C of the [Food and Drug Regulations](#) as described in the "[Good Manufacturing Practices Guidelines, 2009 Edition Version 2 \(GUI-0001\)](#)". Importers should have evidence (e.g. technical agreements) that their suppliers in the non-MRA countries have equivalent requirements for sampling and testing of raw materials used in finished products imported from non-MRA countries.

Manufacturing Control - C.02.011 & C.02.012

Q.1 Can a single lot number be assigned to two or more co-mingled lots of bulk finished drug products packaged during the same run?

A.1 The "[Good Manufacturing Practices Guidelines, 2009 Edition Version 2 \(GUI-0001\)](#)" require that each batch must be identified by an individually numbered manufacturing batch document, each lot or batch of the finished product shall be fully tested against the specification and retained samples for each lot or batch shall be kept. Packaging of multiple lots of bulk finished drug product in a single packaging run with one lot number should be done only in exceptional circumstances and should be well documented with appropriate justification. The shortest expiry date of all the lots packaged must be indicated on the label. In case of a product recall, the company must recall the entire lot comprising all the sub-lots.

Q.2 What is the acceptable deviation in physical counts of finished product stock?

A.2 The allowable deviation between physical counts versus counts as per records (including computer records) should be zero. All finished product stock must be fully accounted for and records of distribution and disposition must be maintained. Any deviations from physical counts versus expected counts as per the records, should be investigated and the results of such investigations should be documented.

Q.3 When are independent checks by another operator necessary?

A.3 The "[Good Manufacturing Practices Guidelines, 2009 Edition Version 2 \(GUI-0001\)](#)" indicate that a number of measures be taken to maintain the integrity of a drug product from the moment the various relevant raw materials enter the plant to the time the finished dosage form is released for sale. These measures seek to eliminate as many sources of error as possible so that only those drugs which have met established specifications are distributed.

One of the approaches proposed to achieve this goal is to have written procedures that ensure that each ingredient added to a batch is subjected to one or more checks for identity and quantity by qualified personnel.

If by its design, construction, operations and security features the procedure is such that the company assures that it is impossible to make an error, an independent check by another operator may not be considered necessary.

Checks for identity and quantity of dispensed materials also require independent checks by a second individual.

However, independent checks that materials have been added to the batch have traditionally been assumed to take place at the time of actual addition of the materials.

Other means of verifying the addition of materials may be considered. One alternative involves checking staged materials in the immediate compounding area prior to starting processing and then afterwards, verifying the empty containers before clearing the compounding area. This would be in conjunction with the use of individual processing rooms, otherwise we would need to be satisfied that there was very good separation of compounding operations.

Q.4 What are the expectations on label accountability?

A.4 It is expected that sufficient controls are in place to ensure that correct labels are applied during a labelling operation and that printed packaging materials are accounted for.

One acceptable means of meeting this requirement is to issue an accurately counted number of labels. That number should be reconciled with the number of labels used, damaged and returned to stock.

In theory, the target set in your procedure should be "0" deviation for labels and other printed packaging materials. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units packaged is investigated and satisfactorily accounted for before release.

Q.5 Is verification of empty containers an acceptable check for addition of ingredients?

A.5 Yes. It is acceptable to check staged materials prior to and after processing as a method of checks for addition through verification of empty containers.

The preferred method for conducting addition checks is by direct observation by the verifier. The verification of empty containers is an acceptable alternative, but only where stringent controls exist regarding the handling of dispensed raw materials.

Such controls include:

- assurance that a dispensed raw material does not end up in the wrong batch; locked portable cages are being used by some firms and only pertinent cages are permitted in the room at the same time.

- adequate operator awareness, training and motivation; the operator has to assure that additions are performed in the proper sequence; any spillage of raw materials must be promptly reported.

- pre and post checking should be performed by qualified personnel and whenever possible should be the same person.

- the post processing check must be performed prior to removal of any material from the area.

Q.6 Are quarantine and release stickers required on all containers of raw materials and packaging materials?

A.6 Quarantine and release stickers are required on all containers of raw materials and packaging components to identify status when a physical quarantine/release system is used.

However, such stickers are not required when a validated electronic quarantine system which effectively prevents the possibility of inadvertent use of unreleased material is in place.

When fully computerized storage systems are used, backup systems should be available in case of system failure.

Q.7 Is an answering machine acceptable for recall activation outside normal working hours?

A.7 A telephone answering machine may be used as part of the provisions for off-hours product recall activation. It should provide information on who to contact, their phone numbers, etc. Its use, functions and monitoring requirements should be included in the written procedures.

Q.8 Is it necessary to document quantities by lot numbers of finished stock destroyed?

A.8 For products returned to the distributor's facility for destruction due to reasons such as damaged or expired product, it may not be mandatory to document the quantities destroyed by lot number.

For products returned following a recall, it is mandatory to document the returns by lot number as it is a requirement to perform a final reconciliation.

If an establishment recall procedures depend on dates of first and last sale of a given lot, records of destruction by lot numbers may provide necessary information pertaining to accountability per lot.

Q.9 Is there a standard on what should be stated in a recall procedure?

A.9 Section C.02.012(1)(a) of the *Food and Drug Regulations* requires that every fabricator, packager/labeller, distributor, importer, and wholesaler of a drug maintains a system of control that permits complete and rapid recall of any lot of batch of the drug that is on the market. Such a system must be tailored to an individual organization and operation.

A written recall system should be in place to ensure compliance with Section C.01.051 of the *Food and Drug Regulations* and should include the requirements outlined in Interpretations 1.1 to 1.11 under Section C.02.012 Manufacturing Control of the "[Good Manufacturing Practices Guidelines, 2009 Edition \(GUI-0001\)](#)". Additional information is available in the "[Recall Policy \(POL-0016\)](#)" and the document entitled "[Product Recall Procedures](#)".

Q.10 Under what circumstances must one initiate a recall?

A.10 Please refer to the "[Recall Policy \(POL-0016\)](#)" and the document entitled "[Product Recall Procedures](#)".

Q.11 May firms omit second person component weight check if scales are connected to a computer system?

A.11 No, for an automated system that do not include checks on component quality control release status and proper identification of containers.

Yes, for a validated automated system with bar code reader that registers the raw materials identification, lot number and expiry date and that is integrated with the recorded accurate weight data.

Q.12 For a contract fabricator, is it a requirement to test the raw materials offered by customers?


A.12 Testing of raw materials (RM) is a responsibility of the fabricator. Therefore, an observation will be made to a fabricator for not testing a particular RM (even when this RM is provided by the client) if he is not excluded by his client according to a contract. Interpretation 3.2 under Section C.02.012 Manufacturing Control covers the written agreements with regard to the fabrication, and packaging/labelling among the parties involved, and Interpretation 6.10 under Section C.02.015 Quality Control Department covers the written agreements with regard to the testing among the parties involved. If no such agreement is in place, the observation will be made against the party responsible according to the Good Manufacturing Practices.

Q.13 If the customer asks a contract fabricator not to test a finished product, is it necessary for the contract fabricator to test the product?

A.13 Interpretation 3.2 under Section C.02.012 Manufacturing Control covers the written agreements with regard to the fabrication, and packaging/labelling among the parties involved, and Interpretation 6.10 under Section C.02.015 Quality Control Department covers the written agreements with regard to the testing among the parties involved. If no such agreement is in place, the observation will be made against the party responsible according to the Good Manufacturing Practices.

Q.14 Is a contract fabricator or packager responsible for qualification of utilities and systems and cleaning validation or is it the responsibility of the distributor? And what about the validation of the manufacturing/packaging process and test methods?

A.14 The contract fabricator is responsible for the qualification of utilities and systems and cleaning validation as those requirements are not product specific.

For process validation and test method validation, the main responsibility rests with the distributor, according to Section C.02.003 of the  *Food and Drug Regulations*. The contract fabricator, packager or tester retains responsibility in terms of process or test methods validation unless a written agreement is signed by both parties that excludes the responsibility of the contract fabricator, packager or tester to perform validation activities.

Q.15 How long in advance can the raw materials be weighed?

A.15 It is acceptable to weigh the raw material (RM) in advance of the scheduled date of production. However, the firm should be able to demonstrate that the materials and design of the containers in which the RM are weighed and kept will not alter their quality, the characteristics of the RM must also be taken into consideration. Interpretation 2 of Section C.02.026 Samples may provide guidance to this effect. Pre-weighed material should be appropriately labelled to ensure traceability. A system should be in place to ensure that the material is still suitable for use on the date of manufacturing.

Q.16 If a licensed packager/labeller is packaging a drug for a foreign establishment which is not intended to be sold in Canada as described under Section 1.0 of "Conditions for Provision of Packaging/Labelling Services for Drugs under Foreign Ownership (GUI-0067)", should this foreign site be listed on the licence of the packager/labeller?

A.16 No. Since this drug would not be sold by the packager/labeller, this establishment would not be considered as an importer under Division 1A of the *Food and Drug Regulations* and thus, this site would not have to be listed on the licence of the packager/labeller. However, the packager/labeller would still need to fulfil all the requirements outlined under Section 4.0 of GUI-0067 that is: obtaining evidence of GMP compliance of the foreign site and supplying the proper information to Health Canada within the prescribed time frame.

Q.17 A Canadian firm does business with a foreign company, and that foreign company contracts out the fabrication, packaging and testing of a product. Is it acceptable to only have a written agreement between the Canadian firm and the foreign company, and not with the contract company?

A 17 In this case, no subcontracting of any work should occur without written authorization from the Canadian firm. In the event of subcontracting, there should be a written agreement between the contracting and subcontracting parties (e.g., contract between Canadian firm and foreign company, foreign company and subcontractor). Copies of the relevant agreements should be available to the Canadian firm.

All establishments conducting licensable activities must hold an Establishment Licence (EL) or be listed on an importer's EL. As per Interpretation 3 under C.02.012 Manufacturing Control and Interpretation 6.10 under C.02.015 Quality Control Department of the "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)", all arrangements for external fabrication, packaging/labelling, and testing are in accordance with the marketing authorization for the drug product concerned, and there is a written agreement covering all activities between the parties involved.

Q.18 What are the expectations surrounding a firm's management review of the Annual Product Quality Review (APQR)?

A.18 Senior management should be aware of significant outcomes from the APQR process and dedicate the resources to address the identified concerns. Evidence to demonstrate that senior management has been made aware could include such things as meeting agendas and/or minutes, quarterly reports, management sign-off of APQR reports, etc.

Q.19 Do all products as described in Interpretation 51 (Regular periodic or rolling quality reviews of all drugs) include low risk Category IV products?

A.19 Yes, we do expect to see Annual Product Quality Reviews completed for Category IV products.

Q.20 For biologics, for which annual reports are already being prepared by fabricators, is a separate APQR required?

A.20 There are some gaps between the information required by the Yearly Biologic Product Reports (YBPR) as described in section 5.1 of Health Canada's Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs, and the Annual Product Quality Review. For example: review of the adequacy of any equipment corrective actions, qualification status of relevant equipment and systems (For example, HVAC, water, compressed gases), contractual agreements, roles/responsibilities of the Quality Control department in APQR, etc. The YBPR would be acceptable providing that an Addendum is available addressing those aspects not covered by the YBPR.

Q.21 Is an importer only responsible for reporting on batches which are physically received/ imported for sale in Canada?

A.21 No. The scope of the APQR should extend to all batches made using the same process, facilities and formulation as the imported product.

Q.22 In C.02.011 Manufacturing Control, Interpretation 51.9 states: "A review of agreements to ensure that they are up to date" and Interpretation 54 states: "Where required, there should be an agreement in place between the various parties involved (For example, importer and fabricator) that defines their respective responsibilities in producing and assessing the quality review and taking any subsequent corrective and preventative actions."**Do these statements mean that an importer should have a quality agreement with the fabricator and this agreement should be reviewed yearly?**

A.22 Yes. The importer should have a quality agreement with the fabricator (outlining responsibilities referencing APQR, etc) and that agreement should be reviewed at least once a year, and updated as necessary.

Quality Control Department - C.02.013, C.02.014 & C.02.015**Q.1 If a product fails its particulate matter specifications, can it be released for sale?**

A.1 No. The particulate matter requirement is treated in the same way as any other specification: failure would constitute non-compliance with the labelled standard.

Q.2 Are the United States Pharmacopoeia (USP) general notices enforceable?

A.2 Yes. The USP General Notices provide in summary form the basic guidelines for interpreting and applying the standards, tests, assays, and other specifications of the USP so that these general statements do not need to be repeated in the various monographs and chapters throughout the book.

Where exceptions to the General Notices exist, the wording in an individual monograph or general test chapter takes precedence.

This concept is further emphasized in the introduction to the General Information chapters which states, "The official requirements for Pharmacopeial articles are set forth in the General Notices, the individual monographs, and the General Tests and Assays chapters of this Pharmacopeia." The General Tests and Assays chapters are those numbered lower than 1000.

Q.3 If a lot meets United States Pharmacopoeia (USP) specifications but fails the firm's internal specifications, can it be released?

A.3 If a lot does not meet its declared release specifications, then the lot should not be released. Where more stringent internal specifications act as an alert limit and not as the basis for release, then the lot may be released after investigation and justification provided it meets its release specifications.

Q.4 Is it acceptable for firms to export expired drugs for charity?

A.4 No. While it is recognized the dire need for drugs in distressed parts of the world, once the expiration date has passed there is no assurance that the drugs have the safety, identity, strength, quality and purity characteristics they purport or represent to possess. As such, expired drugs are considered adulterated and their introduction or delivery for introduction into commerce is prohibited.

Q.5 Explain the United States Pharmacopoeia (USP) measurement uncertainty (MU) requirement for balances.

A.5 USP General Chapter <41> Weights and Balance states a weighing device providing accurate weighing for assay and test is to have MU of less than 0.1% of the reading and gives an example of 50 mg \pm 50 μ g as acceptable. To qualify MU of a balance, an appropriate National Institute of Standards & Technology (NIST) traceable weight within the weighing range of the balance is weighed 10 times or more. The resulting weights are calculated so that three times the calculated standard deviation divided by the amount weighed should be less than 0.001.

For different balance class designations and detailed information on weights and balance, the USP General Chapter <41> is to be consulted.

Q.6 Can an older version of an official method be used or must the most updated version always be used?

A.6 In resolving issues of conformance to an "official standard", the most up to date version of the analytical method is the method that must be used to determine compliance.

Q.7 What is the Inspectorate's position on the use of secondary reference standards (RS) and what are the conditions for the use of secondary reference standards?

A.7 While the Inspectorate recommends the use of the official standards for the analysis of compendia articles, the use of a secondary RS is acceptable if each lot's suitability is determined prior to use by comparison against the current official reference standard and each lot is requalified periodically in accordance with a written protocol. The protocol should clearly address the receipt, storage, handling and use of primary reference standards, the purification of secondary standards, and their qualification against official reference standards.

Q.8 Is it acceptable to use a third party lab's available pharmacopeial reference standard to qualify an establishment's secondary standard?

A.8 This practice is acceptable providing the contract testing lab has an Establishment Licence (EL) and has been audited by the client to demonstrate its capability to qualify the secondary standard (i.e., the official standard and the proper equipment is available on the tester's premises, the method

used has been validated, etc.). Transfer of the standard between the sites should be under controlled conditions.

Q.9 What is the Inspectorate's position on the use of loose work sheets as opposed to bound notebooks for the purpose of recording laboratory data?

A.9 The recommended method of recording laboratory data is a bound book but the use of loose work sheets would be acceptable as long as it is controlled by a system or a procedure to ensure that all raw data are true and accurate, properly recorded and captured, adequately maintained and easily retrievable. The system should also provide accountability and traceability of work sheets.

Q.10 It is generally accepted in the industry to perform process validation on three consecutive lots. How does the Inspectorate view validation when reworking is required (i.e., three consecutive incidents will never happen)?

A.10 Reworking of a batch should be a very rare occurrence. As such, validation of reworking is not considered mandatory as it is not generally feasible. The reworking should be carried out in accordance with a defined procedure approved by Quality Control (QC) and with the conditions described in Interpretation 6 of Section C.02.014 Quality Control Department. This procedure should include supplementary measures and testing during the reworking operations to ensure that the quality of the final product is not compromised.

It is mandatory that rework proposals and reworked product also be fully investigated with respect to impact on release characteristics and potential impact on bio-availability. Changes in formulation due to reworks including the incorporation of additional lubricant or dissolution aid or additional critical processes may require comparative bio-availability studies. Furthermore concomitant stability studies must be undertaken on reworked batches to ensure that critical characteristics are not compromised with time due to the rework.

Q.11 Is it mandatory for the approval of a procedure to sign each page or is it acceptable to only sign the first page?

A.11 It is not mandatory for the approvers to sign each page of the procedure. It would also be acceptable to only sign the last page.

Q.12 If we perform a Total Aerobic Count (TAC) of purified water and that we identify each species found (if any) during the TAC, showing the absence of the two pathogens, is it required to perform a specific test to show the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*?

A.12 Yes, specific tests are required to show the absence of the two pathogens if the specific tests are in the purified water specification to support finished product quality. The species specific tests should follow a compendial method.

Packaging Material Testing - C.02.016 & C.02.017

Q.1 What is the Inspectorate's position on 2-mercaptobenzothiazole (MBT) in rubber closures?

A.1 MBT is sometimes used in the manufacture of rubber stoppers used as closures for vials or as components of syringes. Due to the concerns about the potential toxicity of MBT, its use in the manufacture of packaging materials that are in direct contact with injectable drugs is not permitted.

Q.2 Is it necessary to include a chemical identification test in a specification for a packaging component (such as a plastic bottle)? Must this chemical identification (ID) be conducted for each lot received? Would vendor certification be considered an acceptable substitution for testing upon receipt?

A.2 If the type of material is described on the Certificate of Analysis (C of A) and if a specific test has been performed by the fabricator of the packaging materials confirming the identity of the starting polymer used to manufacture a specific lot, it is not necessary to repeat the chemical ID (such as Infra-Red). But each lot of packaging materials should be visually examined to confirm the identity.

Q.3 Can industrial grade nitrogen be used as a blanketing agent during the manufacture of a drug product?

A.3 No. Any gas used as a blanketing agent should be of compendial standard.

Q.4 If nitrogen is used as blanket in the manufacturing/ filling of parenteral drugs, is it required to test the identity of all the cylinders if the nitrogen supplier has been audited?

A.4 Interpretation 6.1 under C.02.009 Raw Material Testing of the "[Good Manufacturing Practices Guidelines, 2009 Edition Version 2 \(GUI-0001\)](#)", specifies that each container of a lot of a raw material is tested for the identity of its contents using a specifically discriminating identity test. Interpretation 6.3 allows for testing only a proportion of the containers however Interpretation 6.3.2 specifies that Interpretation 6.3 does not apply when the raw material is used in parenterals. Therefore, in response to the question, yes, it is required to test the identity of all the cylinders of nitrogen used as a blanket agent in the manufacturing/filling of parenterals drugs.

Finished Product Testing - C.02.018 & C.02.019

Q.1 Do bacteriostasis and fungistasis testing have to be performed for each lot of product in reference to the United States Pharmacopoeia (USP) sterility test?

A.1 No. This needs to be established only once for a specific formulation to determine the suitable level of inoculate for that product. If the formulation has not changed for a number of years, periodic verification can be done as microorganisms become resistant to preservatives in a formulation.

Q.2 Does the Inspectorate encourage the use of environmental isolates for preservative effectiveness testing?

A.2 While the use of environmental isolates in addition to the specified compendia cultures is acceptable, the use of environmental isolates alone is not acceptable.

Q.3 What are the Inspectorate's expectations for process parametric release for foreign and Canadian manufacturers?

A.3 Further information is available in the document entitled "[Annex 17 of the Current Edition of the Good Manufacturing Practices Guidelines - Guidance on Parametric Release \(GUI-0046\)](#)". Please note that requests will be considered only for terminally sterilized drugs in their immediate containers and following submission and approval of evidence acceptable according to this guidance.

Q.4 Should an inspector observe and question a technician's analytical work?

A.4 An inspector may verify if the laboratory staff is qualified to carry out the work they undertake. This could occasionally include the observation of what the laboratory technicians are performing and question their actual analytical work in conjunction with standard operating procedures (SOP), methods or equipment used.

Also, inspectors will frequently examine testing data from the laboratory for format, accuracy, completeness, and adherence to written procedures. These matters would usually be regarded as requirements under Section C.02.015 Quality Control Department. The general requirements are outlined in Interpretation 6. Laboratory supervisors must sign off subordinates work as per Interpretation 6.3.

Q.5 Does the official method DO-25 apply to tablets labelled as being professed or as manufacturer's standard?

A.5 Section C.01.015 of the [Food and Drug Regulations](#) specifies requirements relating to tablet disintegration times. These regulations require that all drugs in tablet form, intended to be swallowed whole, disintegrate in not more than 60 minutes when tested by the official method.

The regulations also prescribe a specific disintegration requirement and test for tablets which are enteric coated. Subsection (2) specifies conditions where subsection (1) requirements for DO-25 are not required, i.e., (e) drug demonstrated by an acceptable method to be available to the body, and (f) tablets which are for example extended release. Refer to C.01.011 and C.01.012.

The Inspectorate has no objection to the use of an alternate disintegration or dissolution method to demonstrate compliance with the prescribed release requirements provided that the method had been properly validated. It is understood the DO-25 is not generally used for new drugs.

Q.6 Do tests for impurities have to be repeated for finished products if they have been done on the raw materials?

A.6 The sponsor may have evidence that a related impurity present in the drug product is a previously identified/qualified synthetic impurity. In this case, no further qualification for that impurity is required at the drug product stage. The concentration reported for the established synthetic impurity may be excluded from the calculation of the total degradation products in the drug product, and should be clearly indicated as such in the drug product specifications. Evidence should be provided in the submission demonstrating the related impurity is indeed a synthetic impurity (e.g., by showing constant levels during accelerated and/or shelf-life stability studies and confirmation by providing chromatograms of spiked samples). In cases where the methodology applied to the drug substance and drug product differs, the claim should be confirmed by appropriate studies and the results submitted (e.g., using actual reference standards for that compound).

For further information regarding the control of impurities, please consult [Impurities in New Drug Substances - ICH Q3A \(R\)](#) and [Impurities in New Drug Products - ICH Q3B \(R\)](#).

Q.7 What are the minimum testing requirements for solid dosage drugs?

A.7 The testing requirements for solid dosage form products include description, identification, purity, and potency and other applicable quality tests depending on the dosage form (e.g., dissolution/disintegration/drug release, uniformity of dosage units, etc.).

For new drugs, the minimum testing requirements have to be approved by the review Directorates.

Q.8 What are the standards other than the United States Pharmacopoeia (USP) that have official status in Canada?

A.8 The acceptable standards are described in [Schedule B of the Food and Drugs Act](#) ;

- European Pharmacopoeia (Ph.Eur.)
- Pharmacopée française (Ph.F.)
- Pharmacopoeia Internationalis (Ph.I.)
- The British Pharmacopoeia (B.P.)
- The Canadian Formulary (C.F.)
- The National Formulary (N.F.)
- The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals
- The United States Pharmacopoeia (U.S.P.)

Trade standards are also acceptable under certain conditions.

Q.9 Should compendial test methods be validated?

A.9 Since compendial methods cannot encompass all possible formulations of a drug product, the applicability of a compendial method to a company's particular formulation of a drug product must be demonstrated. It must be determined that there is nothing in the product that causes an interference with the compendial method or affects the performance of the method. It must also be established that the impurities that would be expected from the route of synthesis or formulation are controlled by the compendial method.

The main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose.

For guidance on validation of analytical procedures, please refer to [Text on Validation of Analytical Procedures - ICH Q2A](#) and [Validation of Analytical Procedures - ICH Q2B](#).

Q.10 Must all identification tests stated in a compendial monograph be performed?

A.10 Yes, all tests stated in the monograph must be performed.

Q.11 Are solid dosage drugs exempted from dissolution testing if sold under a manufacturer's standard?

A.11 No, solid dosage drugs should include a routine test for monitoring release characteristics (e.g., dissolution).

Q.12 Do products labelled as United States Pharmacopoeia (USP) have to be tested as per the USP test methods?

A.12 No. An alternate method can be used, but the distributor must demonstrate that USP drugs comply with USP specifications when tested by USP methods. If an alternate method is used, it must be fully validated and results from a correlation study should be available.

Q.13 What should be the calibration frequency for a dissolution apparatus used with both baskets & paddles?

A.13 The "[Good Manufacturing Practices Guidelines, 2009 Edition Version 2 \(GUI-0001\)](#)" call for equipment calibration at suitable intervals. Although specific time periods are not given, equipment should be calibrated at a frequency necessary to ensure reliable and reproducible results and covered in the firm's standard operating procedures (SOP). The firm may consult the apparatus manufacturer's manual for guidance. Historical or validation data may also be used by the firm to support an appropriate calibration frequency.

In case of any event that might change operating characteristics of equipment, such as maintenance or moving it, it should be calibrated as required.

Q.14 In performing system suitability as per United States Pharmacopoeia (USP) <621>, do all replicate injections have to be completed before any analyte sample injections are made?

A.14 No.

Q.15 Is routine product pH testing required for endotoxin (*limulus amoebocyte lysate* - LAL) testing?

A.15 No, provided that the method is validated and the firm has not committed to such testing in a new drug submission.

Q.16 Is the use of recycled solvents for high performance liquid chromatography (HPLC) columns acceptable?

A.16 Yes, provided that appropriate validation studies have been performed.

Q.17 If one lot of a product made in a Mutual Recognition Agreement (MRA) country is split into two separate shipments, is it mandatory for the importer to obtain separate manufacturer's batch certificate for each shipment?

A.17 No. However, the importer should demonstrate that the conditions of transportation and storage applicable to this product have been met for each shipment.

Q.18 Is it acceptable to perform the testing, including the potency, before packaging or is it mandatory to perform this testing after packaging?

A.18 Other than the Identity testing which must be performed after packaging, as per Interpretation 1 under C.02.019 Finished Product Testing, there is no specific requirement to perform the other tests after packaging including potency. In such cases, the manufacturing process must be validated to demonstrate that the packaging / filling operation does not alter the quality of the product (including potency). These validation data must also demonstrate that the homogeneity of a product is maintained by appropriate means throughout the entire filling process for dosage forms such as lotion, creams or other suspensions. For parenteral, ophthalmic, and other sterile products, at least identity and sterility testing must be performed on the product in the immediate final container.

For the requirement to perform the identity testing after packaging, the unique identifier principle can be used as long as the chemical / biological identity test has been performed after the unique identifier is applied to the product.

Q.19 A product is manufactured in a non-Mutual Recognition Agreement (non-MRA) country, then shipped in bulk in a MRA country where it is packaged and tested before being released and exported to Canada. Would the testing exemption provided by Interpretation 4 under C.02.019 Finished Product Testing apply?

A.19 No.

Records - C.02.020, C.02.021, C.02.022, C.02.023 & C.02.024

Q.1 Must standard operating procedures (SOP) referenced in master production documents (MPD) be available at the importer's premises?

A.1 Procedures related to critical processes must be available, whether or not they are referenced in the MPD.

Q.2 Can chromatograms be stored on disc instead of retaining the hard copy?

A.2 Yes, refer to the Interpretation under Section C.02.020 to C.02.024 Records.

Q.3 Does the person in charge of quality control have to sign Quality Control (QC) data and documents?

A.3 QC data and documents must be signed by the person in charge of QC or by a designated alternate as per Interpretation 1.4 of Section C.02.006 Personnel, or Interpretation 2.2 in the case of a wholesaler. The person in charge remains accountable for the tasks delegated and retains the necessary authority.

Q.4 According to Section C.02.020 Records, documents to be kept by the fabricator, packager/labeller, distributor and importer must be stored on their premises in Canada.

In the case of a distributor or importer particularly, these documents are sometimes kept only on the premises of a consultant hired to provide Quality Control (QC) services, therefore they are not available on the premises of the distributor or importer at the time of the inspection. Is this practice acceptable?

A.4 No. All documents required under Division 2 of the *Food and Drug Regulations* must be available on the premises of the distributor or importer. Exceptionally, the consultant may bring a file home for a short time to review it but if at the time of the inspection, required documentation are not available on the premises of the distributor or importer, an observation to this effect will be made in the report. In some cases, this could also lead to a non-compliant rating.

Q.5 If electronic signature is not validated, must the signed paper copy be available?

A.5 Yes. The signed paper copy should be available if the electronic signature system has not been validated.

Q.6 Do wholesalers need to validate their computerized systems used for GMP activities (for example, recall)?

A.6 Yes, wholesalers need to validate their computerized systems used for GMP activities. See Interpretation 1 under C.02.020-024 Records of the "**Good Manufacturing Practices, 2009 Edition, Version 2 (GUI-0001)**".

In addition, routine quality system functions carried out in a wholesaling operation are indicated under sections C.02.004 Premises, C.02.006 Personnel, C.02.012 Manufacturing Control, C.02.013, C.02.014 and C.02.015 Quality Control Department including:

- tracking of customer orders and product distribution for the purpose of carrying out an effective and timely recall
- maintaining material status control ie. released, rejected, quarantine, returned and recalled products, etc.
- accountability of stock/inventory control (related to recall capability)
- expiry date control (to ensure expired or soon to be expired products are not distributed)
- proper storage of drug products (environmental control) i.e. temperature mapping, monitoring of storage temperature to ensure drug label storage conditions are met
- deviation handling i.e. temperature excursion, temperature alarm and notification, procedure deviation, etc. - processing of returned drugs
- complaint handling (product or operation related)
- self inspection

Companies may choose to control these functions by means of a computerised system. There is no specific regulation requiring computer validation. However, this requirement is implied. When computer or automated systems are used to control and maintain quality systems functions; to maintain records required by regulations and to demonstrate compliance with regulatory requirements for records (C.02.021,C.02.022,C.02.023,C.02.024), the system must be able to provide and maintain data integrity. Thus, the system should be validated for its intended use. Validation activities and results are to be documented.

Samples - C.02.025 & C.02.026


Q.1 What is considered an adequate sample when tank loads of a raw material is received?

A.1 As per Interpretation 3 under Section C.02.025-C.02.026 Samples, the retained sample should represent at least twice the amount necessary to complete all required tests. For bulk materials received in tankers, the retained sample should be taken before being mixed-up with the unused quantities still present in the storage tank.


Q.2 A pressurized tanker of hydrocarbon raw materials (isobutan, propane, etc.) is normally sampled and approved before pumping. What is the current Inspectorate policy for sample retention given the inherent risks generated by these flammable gases under pressure?

A.2 The intent of regulation C.02.030 is applied to these cases. Samples of pressurized raw materials are not expected to be retained by manufacturers.

Q.3 If a product is fabricated in Canada and exported outside of Canada (the product is not sold on the Canadian market), are samples of this finished product to be retained in Canada?

A.3 No. This Canadian site is a contract fabricator and not a distributor. Subsection C.02.025 (1) of the  *Food and Drug Regulations* (FDR) requires that a sample of each lot of the packaged/labelled drug be kept by the distributor and the importer (not the fabricator). This is also applicable if the Canadian fabricator manufactures a product for a Canadian distributor (Drug Identification Number (DIN) owner). While subsection C.02.025(2) of the FDR for retained samples of raw materials, the requirement applies to the fabricator (the person that transforms the raw material into a finished product), not the distributor. Subsection C.02.025(2) of the FDR for retained samples of raw materials, applies to the fabricator (the person that transforms the raw material into a finished product), not the distributor.

Q.4 If a product is fabricated in Canada, and contract packaged by another company in Canada and then exported outside of Canada (the product is not sold on the Canadian market), who is responsible for retaining samples of the finished products?

A.4 The Canadian fabricator and the Canadian packager/labeller are not responsible for retaining samples of the finished product. Subsection C.02.025 (1) of the  *Food and Drug Regulations* (FDR) requires that a sample of each lot of the packaged/labelled drug be kept by the distributor and the importer (not the fabricator). This is also applicable if the Canadian fabricator manufactures a product for a Canadian distributor (Drug Identification Number (DIN) owner). This could vary according to the requirement of each health authority. On the other hand, both parties (Canadian fabricator or packager/labeller) could negotiate a written contract or agreement with the foreign client (the distributor/owner of the product) in order to clearly mention who will be responsible to keep the retained samples of the finished product, as long as this is acceptable to the health authority of that country. Each country could have their own regulatory requirement.

Stability - C.02.027 & C.02.028

Q.1 Do batches have to be tested for preservatives at initial release and then in the continuing stability program?


A.1 Finished products where antimicrobial agents are added to preparations such as multiple dose injections, topical creams, and oral liquids, an assay with limits should be included in the specifications.

An antimicrobial preservative effectiveness testing is performed during the development phase of the product to establish the minimal effective level of preservatives that will be available up to the stated expiry date, and for which a single regular production batch of the drug is to be tested for antimicrobial preservative effectiveness at the end of the proposed shelf life. Once the minimal effective preservative level has been determined, all lots of any preservative containing dosage form included in the stability program must be tested at least once at the expiry date for preservative content. For sterile drugs, the declaration of preservatives on the label is mandatory and those should be treated as for active ingredients (i.e., tested for preservative content at pre-established control points for those batches enrolled in of the continuing stability program). Where the lower limit of the preservative is less than 90 percent of label claim, the challenge test should be performed on samples at or below the lower limit. The challenge test need not be included in the specifications, provided that an assay for the preservative is included.

Q.2 Can it be assumed that United States Pharmacopoeia (USP) chromatographic assay methods are stability indicating?

A.2 No.

Q.3 Is it acceptable to place an expiry date on a bottle cap instead of on the bottle label?

A.3 No. Please refer to Section C.01.004(c)(v) of the  *Food and Drug Regulations*. The expiration date must appear on any panel of the inner and outer label.

Q.4 When the labelled expiration date states only the month and year does it mean the end of the month?

A.4 Yes. The product should meet approved specifications up to the last day of the specified month.

Q.5 Can accelerated stability data of less than three months be used?

A.5 Accelerated stability studies of any length are considered as preliminary information only and should be supported by long term testing.

The assignment of expiry dates should be based on long term testing.

Q.6 Should drugs packaged into kits and subsequently sterilized, be tested for stability?

A.6 Yes. These operations are part of manufacturing. For drugs that are packaged into trays or kits and the resulting package is sterilized prior to being marketed, data should be available to demonstrate that the sterilization process does not adversely affect the physical and chemical properties of the drug. The testing should be sensitive enough to detect any potential chemical reactions and/or degradation, and the test results should be compared with test values obtained prior to sterilization.

5.2 Sterile Products

Q.1 Does the supervisor of a sterile product manufacturing facility need to have a degree in microbiology?

A.1 Section C.02.029(b) of Division 2 of the *Food and Drug Regulations* requires that "...a drug that is intended to be sterile shall be produced under the supervision of personnel trained in microbiology...". The expression "trained in microbiology" does not mean that this person must have a University degree in microbiology. However, the person must have taken university courses in microbiology.

Q.2 If water that has already been used in compounding is later found to contain endotoxins, what actions need to be taken?

A.2 Water can be used for production prior to obtaining microbiological testing results but the results of these tests must be available prior to final release of the product. Good Manufacturing Practices permit release only after raw material and finished product testing is completed and results demonstrate compliance of the product with its specifications.

The appropriate action would include an investigation into:

- i. the potential sources of endotoxins;
- ii. the sanitation and maintenance of the water system.

Q.3 Are sterile products in amber glass and plastic ampoules exempt from 100% visual inspection?

A.3 No. Each final container of injections must be subjected to a visual inspection. The 100% visual inspection test does not limit itself to particulate matter but includes sealing defects, charring, glass defects, underfills and overfills, missing print, etc. Please refer to Interpretation 84 under Section C.02.029 Sterile Products. For parenterals, there are additional requirements for packaging (i.e., the immediate container shall be of such material and construction that visual or electronic inspection of the drug is possible). Please refer to Section C.01.069 of the [EU Food and Drug Regulations](#).

Q.4 What are the requirements in terms of monitoring/testing for the release of sterile gowns to be used in a controlled environment (Grades A or B) when those are obtained from a supplier?

A.4 There is no specific requirements in the "Good Manufacturing Practices Guidelines, 2009 Edition Version 2 (GUI-0001)" for the sterility testing of the protective garments to be worn in Grades A and B areas. However, the sterility cycle used by an outside supplier to sterilize these garments should have been validated according to scientifically sound procedures. Among other aspects, validation should address penetration/distribution studies of the sterilizing medium (gas, radiation, heat, etc.), load patterns of the sterilizers, determination of the Sterility Assurance Level with Bio indicators, etc. Also, the integrity of the outside wrapping in order to maintain sterility should be demonstrated.

Q.5 What are the room classification requirements for the preparation of containers and other packaging materials to be used in the fabrication of sterile products?

A.5 The preparation (cleaning, washing, etc.) of containers and packaging materials is normally performed in a "clean" room (Grades C or D). After these operations, the containers and materials used for drugs sterilized by filtration (and not further subjected to terminal sterilization in their final containers) must be depyrogenated and sterilized before being introduced in the aseptic rooms by the use of double-ended sterilizers or any other validated method. The depyrogenation step can be done using pyrogen-free water for injection (WFI) for the last rinse prior sterilization or by performing the depyrogenation and sterilization in one operation using a dry heat oven. Filling of these products normally takes place in a Grade A with a Grade B background.

For products submitted to terminal sterilization, it is not mandatory to use containers and packaging materials that are sterile but those that are in direct contact with the product should be free of pyrogen. This is usually achieved by using pyrogen-free WFI for the last rinse of these materials unless they are subsequently depyrogenated by another method (e.g., dry heat oven).

In addition, the initial bioburden of these materials should meet pre-established limits (that are based on sound science) and the risk of contamination during their introduction in the filling areas should be kept to a minimum.

Q.6 For the validation of moist heat sterilization cycles, will the new standards include the use of prions as the organism of choice instead of *Bacillus stearothermophilus*?

A.6 At the present time, it is recognized in the scientific and pharmaceutical community that the spores of *Bacillus stearothermophilus* are the organisms of choice for the validation of moist heat sterilization cycles. Validation of such cycles is based on biological indicators containing a known count of organisms in order to determine a lethality factor for a given cycle. Those studies are based on parameters such as the "D" value of certain organisms and also imply a microbiological testing of these indicators at the end of the cycle in order to establish a survival rate. The use of prions (infectious proteins) could be inadequate in that their detection and quantification, which is based on animal models, is very difficult. Moreover, these proteins are very difficult to destroy and could present a danger should they accidentally be spread in a plant.

Q.7 According to the monograph on parenteral products (0520) of the 4th edition (2002) of the European Pharmacopeia (Ph. Eur.), injections for veterinary use with a volume dose of less than 15 mL are exempted from bacterial endotoxins/pyrogen testing by the European Union (EU). Is this interpretation correct? If so, would this EU exemption be applicable in Canada?

A.7 Yes, this interpretation is correct but this exemption is not applicable in Canada.

As per Section C.01.067(1) of the [Food and Drug Regulations](#), it is required that each lot of a drug for parenteral use be tested for the presence of pyrogens using an acceptable method and be found to be non-pyrogenic. The Bacterial Endotoxins and Pyrogen test methods described in the United States Pharmacopoeia (USP) and Ph. Eur. are considered acceptable methods for that purpose. For all parenteral drug products, the Bacterial Endotoxins test should be preferred over the Pyrogen test unless the latter is demonstrated to be justified (more appropriate) or has been approved by a review Directorate. Therefore, the specification of all drug products for parenteral use intended for the Canadian market should include a test for Bacterial Endotoxins or Pyrogens and the EU current "15 mL exemption" is not applicable in Canada.

The only acceptable exemptions are those provided by Section C.01.067(2) (i.e., for parenteral drug products inherently pyrogenic or those which cannot be tested for the presence of pyrogens by either test methods). In other words, not testing a parenteral drug product for the presence of pyrogens would be considered acceptable only if documentation is available demonstrating that the parenteral drug product is inherently pyrogenic or that it cannot be tested by any of the methods.

Q.8 For radiopharmaceuticals, can it be acceptable to verify the integrity of the sterilizing filter only after use and to not perform the pre-filtration integrity testing?

A.8 As per Interpretation 4.7 under Section C.02.029 Sterile Products, the integrity of the sterilizing filter must be verified before and after use. However, the pre-filtration integrity testing for that type of products could lead to radioactive contamination as a result of the venting process of the filter assembly that must be performed before the start of product filtration. This would pose an unacceptable health risk for the operators and could result in disruption of production until the facility is decontaminated. It is therefore acceptable to use two filters of a minimum filter rating of 0.22 micron and to verify the integrity of the sterilizing filters after use only for these products. However, data should be available from the filter manufacturer that the filters are supplied pre-assembled and individually integrity tested by the filter manufacturer.

Q.9 What is the Inspectorate's position on pooling of samples within the same batch (e.g., 7 samples in one pool) for testing for sterility? The European Pharmacopoeia (Ph. Eur.) does not mention explicitly a pooling of samples for testing for sterility.

A.9 It is acceptable if companies pool samples for sterility testing with the membrane filtration method. However, it is not acceptable to pool samples when the direct inoculation method is used. Exceptions can be tolerated, when the volume of the sample-pool does not exceed 10% of the culture medium volume.

6. ICH

6.1 ICH: Q8, Q9 and Q10

A. For General Clarification (1.1)

Q1: Is the minimal approach accepted by regulators?

A1: Yes. The minimal approach as defined in Q8(R2) (sometime also called “baseline” or “traditional” approach) is the expectation that is to be achieved for a fully acceptable submission. However, the “enhanced” approach as described in ICH Q8(R2) is encouraged (Ref. Q8(R2) Annex, appendix 1). (Approved June 2009)

Q2: What is an appropriate approach for process validation using ICH Q8, Q9, and Q10?

A2: The objectives of process validation are unchanged when using ICH Q8, Q9, and Q10. The main objective of process validation remains that a process design yields a product meeting its predefined quality criteria. ICH Q8, Q9, and Q10 provide a structured way to define product critical quality attributes, design space, the manufacturing process, and the control strategy. This information can be used to identify the type and focus of studies to be performed prior to and on initial commercial production batches. As an alternative to the traditional process validation, continuous process verification (see definition in ICH Q8(R2) glossary) can be utilized in process validation protocols for the initial commercial production and for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle. (Approved October 2009)

Q3: How can information from risk management and continuous process verification provide for a robust continual improvement approach under ICH Q8, Q9 and Q10?

A3: Like the product itself, process validation also has a lifecycle (process design, process qualification and ongoing process verification). A risk assessment conducted prior to initial commercial validation batches can highlight the areas where particular focus and data collection could demonstrate the desired high level of assurance of commercial process robustness. Continual monitoring (e.g., via continuous process verification) can further demonstrate the actual level of assurance of process consistency and provide the basis for continual improvement of the product. Quality Risk Management methodologies of ICH Q9 can be applied throughout the product lifecycle to maintain a state of process control. (Approved October 2009)

B. Quality by Design (QbD) Topics (2)

Q1: Is it always necessary to have a design space (DS) or real-time release (RTR) testing to implement QbD?

A1: Under Quality by Design, establishing a design space or using real-time release testing is not necessarily expected (ICH Q8(R2)). (Approved April 2009)

1. Design Space (2.1)

Q1: Is it necessary to study multivariate interactions of all parameters to develop a design space?

A1: No, the applicant should justify the choice of material attributes and parameters for multivariate experimentation based on risk assessment and desired operational flexibility. (Approved April 2009)

Q2: Can a design space be applicable to scale-up?

A2: Yes, when appropriately justified (for additional details, see Q8(R2) Annex section II.D.4 (2.4.4)). An example of a scale-independent design space is provided in the European Federation of Pharmaceutical Industries and Associations (EFPIA) Mock P2 document (EFPIA Mock P2 submission on “Exampain”: Chris Potter, Rafael Beerbohm, Alastair Coupe, Fritz Erni, Gerd Fischer, Staffan Folestad, Gordon Muirhead, Stephan Roenninger, Alistair Swanson, A guide to EFPIA’s “Mock P.2” Document, Pharm. Tech. (Europe), 18, December 2006, 39-44).

This example may not reflect the full regulatory requirements for a scale-up. (Approved April 2009)

Q3: Can a design space be applicable to a site change?

A3: Yes, it is possible to justify a site change using a site independent design space based on a demonstrated understanding of the robustness of the process and an in depth consideration of site specific factors (e.g., equipment, personnel, utilities, manufacturing environment, and equipment). There are region specific regulatory requirements associated with site changes that need to be followed. (Approved April 2009)

Q4: Can a design space be developed for single and/or multiple unit operations?

A4: Yes, it is possible to develop a design space for single unit operations or across a series of unit operations (see Q8(R2) Annex, section II.D.3 (2.4.3)). (Approved April 2009)

Q5: Is it possible to develop a design space for existing products?

A5: Yes, it is possible. Manufacturing data and process knowledge can be used to support a design space for existing products. Relevant information should be utilized from e.g., commercial scale manufacturing, process improvement, corrective and preventive action (CAPA), and development data.

For manufacturing operations run under narrow operational ranges in fixed equipment, an expanded region of operation and an understanding of multiparameter interactions may not be achievable from existing manufacturing data alone and additional studies may provide the information to develop a design space. Sufficient knowledge should be demonstrated, and the design space should be supported experimentally to investigate interactions and establish parameter/attribute ranges. (Approved April 2009)

Q6: Is there a regulatory expectation to develop a design space for an existing product?

A6: No, development of design space for existing products is not necessary unless the applicant has a specific need and desires to use a design space as a means to achieve a higher degree of product and process understanding. This may increase manufacturing flexibility and/or robustness. (Approved April 2009)

Q7: Can a design space be applicable to formulation?

A7: Yes, it may be possible to develop formulation (not component but rather composition) design space consisting of the ranges of excipient amount and its physicochemical properties (e.g., particle size distribution, substitution degree of polymer) based on an enhanced knowledge over a wider range of material attributes. The applicant should justify the rationale for establishing the design space with respect to quality attributes such as bioequivalence, stability, manufacturing robustness etc. Formulation adjustment within the design space depending on material attributes does not need a submission in a regulatory postapproval change. (Approved June 2009)

Q8: Does a set of proven acceptable ranges alone constitute a design space?

A8: No, a combination of proven acceptable ranges (PARs) developed from univariate experimentation does not constitute a design space (see Q8(R2) Annex, section II.D.5 (2.4.5)). Proven acceptable ranges from only univariate experimentation may lack an understanding of interactions between the process parameters and/or material attributes. However proven acceptable ranges continue to be acceptable from the regulatory perspective but are not considered a design space (see ICH Q8(R2) Annex, section II.D.5 (2.4.5)). The applicant may elect to use proven acceptable ranges or design space for different aspects of the manufacturing process. (Approved June 2009)

Q9: Should the outer limits of the design space be evaluated during process validation studies at the commercial scale?

A9: No. There is no need to run the qualification batches at the outer limits of the design space during process validation studies at commercial scale. The design space should be sufficiently explored earlier during development studies (for scale-up, see also section II.B.1 Design Space (2.1), Q2; for lifecycle approach, see section II.A For General Clarification (1.1), Q3). (Approved November 2010)
2. Real-Time Release Testing (2.2)

Q1: How is batch release affected by employing real-time release testing?

A1: Batch release is the final decision to release the product to the market regardless of whether RTR testing or end-product testing is employed. End-product testing involves performance of specific analytical procedures on a defined sample size of the final product after completion of all processing for a given batch of that product. Results of real-time release testing are handled in the same manner as end-product testing results in the batch release decision. Batch release involves an independent review of batch conformance to predefined criteria through review of testing results and manufacturing records together with appropriate good manufacturing practice (GMP) compliance and quality system, regardless of which approach is used. (Approved April 2009)

Q2: Does real-time release testing mean elimination of end-product testing?

A2: Real-time release testing does not necessarily eliminate all end-product testing. For example, an applicant can propose RTR testing for some attributes only or not all. If all critical quality attributes (CQAs) (relevant for real-time release testing) are assured by in-process monitoring of parameters and/or testing of materials, then end-product testing might not be needed for batch release. Some product testing will be expected for certain regulatory processes such as stability studies or regional requirements. (Approved April 2009)

Q3: Is a product specification still necessary in the case of RTR testing?

A3: Yes, product specifications (see ICH Q6A and Q6B) still need to be established and met, when tested.³ (Approved April 2009)

Q4: When using RTR testing, is there a need for stability test methods?

A4: Even where RTR testing is applied, a stability monitoring protocol that uses stability indicating methods is required⁴ for all products regardless of the means of release testing (see ICH Q1A and ICH Q5C). (Approved April 2009)

Q5: What is the relationship between control strategy and RTR testing?

A5: RTR testing, if utilized, is an element of the control strategy in which tests and/or monitoring can be performed as in-process testing (in-line, on-line, at-line) rather than tested on the end product. (Approved April 2009)

Q6: Do traditional sampling approaches apply to RTR testing?

A6: No, traditional sampling plans for in-process and end-product testing involve a discrete sample size that represents the minimal sampling expectations. Generally, the use of RTR testing will include more extensive on-line/in-line measurement. A scientifically sound sampling approach should be developed, justified, and implemented. (Approved April 2009)

Q7: If RTR testing results fail or trending toward failure, can end-product testing be used to release the batch?

A7: No, in principle the RTR testing results should be routinely used for the batch release decisions and not be substituted by end-product testing. Any failure should be investigated and trending should be followed up appropriately. However, batch release decisions should be made based on the results of the investigations. In the case of failure of the testing equipment, please refer to the previous question. The batch release decision should comply with the content of the marketing authorization and GMP compliance. (Approved April 2009)

Q8: What is the relationship between in-process testing and RTR testing?

A8: In-process testing includes any testing that occurs during the manufacturing process of drug substance and/or finished product. Real-time release testing includes those in-process tests that have a direct impact on the decision for batch release through evaluation of critical quality attributes. (Approved June 2009)

Q9: What is the difference between "real time release" and "real-time release testing"?

A9: The definition of real-time release testing in Q8(R2) is "the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically includes a valid combination of measured material attributes and process controls." The term real time release in the Q8(R2), step 2 document was revised to "realtime release testing" in the final Q8(R2) Annex to fit the definition more accurately and thus avoid confusion with batch release. (Approved June 2009)

Q10: Can surrogate measurement be used for RTR testing?

A10: Yes, RTR testing can be based on measurement of a surrogate (e.g., process parameter, material attribute) that has been demonstrated to correlate with an in-process or end-product specification (see ICH Q8(R2); Annex, section II.E (2.5)). (Approved June 2009)

Q11: What is the relationship between RTR testing and parametric release?

A11: Parametric release is one type of RTR testing. Parametric release is based on process data (e.g., temperature, pressure, time for terminal sterilization, physicochemical indicator) rather than the testing of material and/or a sample for a specific attribute. (Approved October 2009)

3. Control Strategy (2.3)

Refer to the definition of control strategy provided in the ICH Q10 glossary:

A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Q1: What is the difference in a control strategy for products developed using the minimal approach vs. "quality-by-design" approach?

A1: Control strategies are expected irrespective of the development approach. Control strategy includes different types of control proposed by the applicant to assure product quality (ICH Q10, section IV.B.1 (3.2.1)), such as in-process testing and end-product testing. For products developed following the minimal approach, the control strategy is usually derived empirically and typically relies more on discrete sampling and end-product testing. Under QbD, the control strategy is derived using a systematic science and risk-based approach. Testing, monitoring, or controlling is often shifted earlier into the process and conducted in-line, online, or at-line testing. (Approved April 2009)

Q2: Are GMP requirements different for batch release under QbD?

A2: No, the same GMP requirements apply for batch release under minimal and QbD approaches. (Approved April 2009)

Q3: What is the relationship between a design space and a control strategy?

A3: A control strategy is required for all products.⁵ If a design space is developed and approved, the control strategy (see ICH Q8(R2), Annex, section IV (4)) provides the mechanism to ensure that the manufacturing process is maintained within the boundaries described by the design space. (Approved April 2009)

Q4: What approaches can be taken in the event of on-line/in-line/at-line testing or monitoring equipment breakdown?

A4: The control strategy provided in the application should include a proposal for use of alternative testing or monitoring approaches in cases of equipment failure. The alternative approach could involve use of end-product testing or other options, while maintaining an acceptable level of quality. Testing or monitoring equipment breakdown should be managed in the context of a deviation under the quality system and can be covered by GMP inspection. (Approved June 2009)

Q5: Are product specifications different for minimal versus QbD approaches?

A5: In principle no, product specifications are the same for minimal and QbD approaches. For a QbD approach, the control strategy can facilitate achieving the end product specifications via real time release testing approaches (see ICH Q8(R2) Annex, appendix 1). Product must meet specification, when tested.⁶ (Approved October 2009)

Pharmaceutical Quality System (3)

Q1: What are the benefits of implementing a pharmaceutical quality system (PQS) in accordance with ICH Q10)?

A1: The benefits are:

- Facilitated robustness of the manufacturing process, through facilitation of continual improvement through science and risk-based postapproval change processes
- Consistency in the global pharmaceutical environment across regions
- Enable transparency of systems, processes, and organizational and management responsibility
- Clearer understanding of the application of a quality system throughout product lifecycle
- Further reducing risk of product failure and incidence of complaints and recalls, thereby providing greater assurance of pharmaceutical product consistency and availability (supply) to the patient
- Better process performance
- Opportunity to increase understanding between industry and regulators and more optimal use of industry and regulatory resources; enhance manufacturer's and regulators' confidence in product quality
- Increased compliance with GMPs, which builds confidence in the regulators

and may result in shorter inspections (Approved April 2009)

Q2: How does a company demonstrate implementation of PQS in accordance with ICH Q10?

A2: When implemented, a company will demonstrate the use of an effective PQS through its documentation (e.g., policies, standards), its processes, its training/qualification, its management, its continual improvement efforts, and its performance against pre-defined key performance indicators (see ICH Q10 glossary on performance indicator).

A mechanism should be established to demonstrate at a site how the PQS operates across the product lifecycle, in an easily understandable way for management, staff, and regulatory inspectors, e.g., a quality manual, documentation, flowcharts, procedures. Companies can implement a program in which the PQS is routinely audited in-house (i.e., internal audit program) to ensure that the system is functioning at a high level. (Approved April 2009)

Q3: Is it necessary to describe the PQS in a regulatory submission?

A3: No, however relevant elements of the PQS (such as quality monitoring system, change control, and deviation management) can be referenced as part of the control strategy as supporting information. (Approved April 2009)

Q4: Will there be certification that the PQS is in accordance with ICH Q10?

A4: No. There will not be a specific ICH Q10 certification program. (Approved April 2009)

Q5: How should the implementation of the design space be evaluated during inspection of the manufacturing site?

A5: Inspection should verify/assess that manufacturing operations are appropriately carried out within the design space. The inspector in collaboration with the assessor, where appropriate, should also verify successful manufacturing operations under the design space and that movement within the design space is managed within the company's change management system (see ICH Q10, section IV. B.3 (3.2), Table III). (Approved April 2009)

Q6: What should be done if manufacturing operations run inadvertently outside of the design space?

A6: This should be handled as a deviation under GMP. For example, unplanned "oneoff" excursions occurring as a result of unexpected events, such as operator error or equipment failure, would be investigated, documented, and dealt with as a deviation in the usual way. The results of the investigation could contribute to the process knowledge, preventive actions, and continual improvement of the product. (Approved April 2009)

Q7: What information and documentation of the development studies should be available at a manufacturing site?

A7: Pharmaceutical development information (e.g., supporting information on design space, chemometric model, risk management) is available at the development site. Pharmaceutical development information that is useful to ensure the understanding of the basis for the manufacturing

process and control strategy, including the rationale for selection of critical process parameters and critical quality attributes, should be available at the manufacturing site. Scientific collaboration and knowledge sharing between pharmaceutical development and manufacturing is essential to ensure the successful transfer to production. (Approved June 2009)

Q8: Can process parameters be adjusted throughout the product lifecycle?

A8: Process parameters are studied and selected during pharmaceutical development and monitored during commercial manufacturing. Knowledge gained could be utilized for adjustment of the parameters as part of continual improvement of the process throughout the lifecycle of the drug product (see ICH Q10, section IV (3)). (Approved June 2009)

D. Impact of New ICH Quality Guidance on GMP Inspection Practices (4)

Q1: How will product-related inspections differ in an ICH Q8, Q9 and Q10 environment?

A1: In the case of product-related inspection (in particular, preauthorization) depending on the complexity of the product and/or process, greater collaboration between inspectors and assessors could be helpful (for example, for the assessment of development data). The inspection would normally occur at the proposed commercial manufacturing site, and there is likely to be greater focus on enhanced process understanding and understanding relationships, e.g., critical quality attributes (CQAs), critical process parameters (CPPs). The inspection might also focus on the application and implementation of quality risk management principles, as supported by the pharmaceutical quality system (PQS). (Approved April 2009)

Q2: How will system-related inspections differ in an ICH Q8, Q9, and Q10 environment?

A2: The inspection process will remain similar. However, upon the implementation of ICH Q8, Q9, and Q10, inspections will have greater focus on (but not only focus on) how the PQS facilitates the use of e.g., quality risk management methods, implementation of design space, and change management (see ICH Q10). (Approved April 2009)

Q3: How is control strategy approved in the application and evaluated during inspection?

A3: Elements of control strategy submitted in the application will be reviewed and approved by the regulatory agency. However, additional elements are subject to inspection (as described in Q10). (Approved October 2009)

E. Knowledge Management (5)

Q1: How has the implementation of ICH Q8, Q9, and Q10 changed the significance and use of knowledge management?

A1: Q10 defines knowledge management as: "Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components." Knowledge management is not a system; it enables the implementation of the concepts described in ICH Q8, Q9 and Q10.

Knowledge management is not a new concept. It is always important regardless of the development approach. Q10 highlights knowledge management because it is expected that more complex information generated by appropriate approaches (e.g., QbD, process analytical technology (PAT) real-time data generation, and control monitoring systems) should be better captured, managed, and shared during product life-cycle.

In conjunction with quality risk management, knowledge management can facilitate the use of concepts such as prior knowledge (including from other similar products), development of design space, control strategy, technology transfer, and continual improvement across the product life cycle. (Approved April 2009)

Q2: Does Q10 suggest an ideal way to manage knowledge?

A2: No. Q10 provides a framework and does not prescribe how to implement knowledge management. Each company decides how to manage knowledge, including the depth and extent of information assessment based on its specific needs. (Approved April 2009)

Q3: What are potential sources of information for knowledge management?

A3: Some examples of knowledge sources are:

- Prior knowledge based on experience obtained from similar processes (internal knowledge, industry scientific and technical publications) and published information (external knowledge: literature and peer-reviewed publications)
- Pharmaceutical development studies
- Mechanism of action
- Structure/function relationships
- Technology transfer activities
- Process validation studies
- Manufacturing experience, e.g.,
 - Internal and vendor audits
 - Raw material testing data
- Innovation
- Continual improvement
- Change management activities
- Stability reports
- Product quality reviews/annual product reviews
- Complaint reports
- Adverse event reports (patient safety)
- Deviation reports, recall Information
- Technical investigations and/or CAPA reports
- Suppliers and contractors
- Product history and /or manufacturing history
- Ongoing manufacturing processes information (e.g., trends)

Information from the above can be sourced and shared across a site or company, between companies and suppliers/contractors, products, and across different disciplines (e.g., development, manufacturing, engineering, quality units). (Approved April 2009)

Q4: Is a specific dedicated, computerized information management system required for the implementation of knowledge management with respect to ICH Q8, Q9, and Q10?

A4: No, but such computerized information management systems can be invaluable in capturing, managing, assessing, and sharing complex data and information. (Approved April 2009)

Q5: Will regulatory agencies expect to see a formal knowledge management approach during inspections?

A5: No. There is no added regulatory requirement for a formal knowledge management system. However, it is expected that knowledge from different processes and systems will be appropriately utilized.

Note: "formal" means: it is a structured approach using a recognized methodology or information technology (IT) tool, executing and documenting something in a transparent and detailed manner. (Approved June 2009)

F. Software Solutions (6)

Q1: With the rapid growth of the new science and risk-based quality paradigm coupled with the IWG efforts to facilitate globally consistent implementation of Q8, Q9, and Q10, a number of commercial vendors are now offering products that are being marketed as "ICH compliant solutions" or ICH Q8, 9, and 10 Implementation software, etc. Is it necessary for a pharmaceutical firm to purchase these products to achieve a successful implementation of these ICH guidances within their companies?

A1: No. The ICH Implementation Working Group has not endorsed any commercial products and does not intend to do so. ICH is not a regulatory agency with reviewing authority and thus does not have a role in determining or defining "ICH compliance" for any commercial products. While there will likely be a continuous proliferation of new products targeting the implementation of these ICH guidances, firms should carry out their own evaluation of these products relative to their business needs. (Approved April 2009)

6.2 FDA and EMA on Design Space Verification

1. Why would a design space be verified during the product lifecycle?

In both Agencies' experience, the design space verification at commercial scale is not necessarily complete at the time of submission of the application but should occur over the lifecycle of the product and process. Initial design space verification often occurs solely at or near the target operating ranges. However, movements from one area to another area within the design space (e.g., re-establishing the Normal Operating Ranges (NOR)) within the approved design space in an unverified area) may pose higher or unknown risks due to potential scale-up effects and/or model assumptions. It is important that these risks are understood and evaluated utilizing an appropriate control strategy, including but not restricted to the controls submitted in the dossier. It is understood that when an applicant demonstrates that a design space is scale independent, then additional risk mitigation steps are not necessary for design space verification.

2. What is the purpose of design space verification at commercial scale?

Design space verification demonstrates that within design space boundaries scale-up effects are under control and do not adversely affect the expected product quality at commercial scale.

3. How is a design space initially developed and verified at commercial scale?

Both Agencies acknowledge that when a design space is established at early stages of product development, it is typically developed based on experiments conducted at laboratory or pilot scale. The confidence in the design space at commercial scale can vary depending on the amount and type of development data generated and the knowledge of the scalability (i.e., the degree of scale dependency of the design space). Design space limits at commercial scale can be based on scale-up correlations demonstrated during development studies and/or experimentation. In addition, design space limits can be challenged with computational simulations. The Agencies further acknowledged that the commercial process is generally operated in a specific area of the design space, sometimes called the NOR (Normal Operating Range). The NOR describes a region around the target operating conditions that contains typical operational variability. Initial process verification often occurs solely within the NOR at commercial scale.

4. How can a design space be verified at commercial scale?

It is not necessary to repeat at commercial scale the experiments initially conducted to define a design space at lab or pilot scale. Furthermore, it is neither necessary to verify entire areas of design space nor to identify the edge of failure. In principle, more than one area of a design space may be verified at the time of submission but the design space can, as appropriate, also be further verified over the product lifecycle. The approach to design space verification over the product lifecycle can be guided by the results of risk assessment on the potential effect of changes to scale dependent parameters on product quality. Depending on the specific change, the potential impact to the product quality, and the ability of the control strategy to detect product failures, the management of the risk can include additional monitoring of quality attributes and/or process parameters not included in the routine control system.

5. How should design space verification protocol be addressed in the submission?

In principle, a design space verification protocol could include the following: list of scale dependent parameters whose impact on the CQAs has not been verified at commercial scale, definition of the potential scale-up risks to the CQAs, discussion of whether the control strategy can address these risks, and description of any additional controls, as needed. EU authorities' expectation is that a protocol for design space verification be submitted in section 3.2.R of the application. At the time of submission, a proposed design space not verified at commercial scale should be accompanied by an appropriate verification protocol. The protocol would be assessed at the time of review. Verification data are managed and documented in the site change management system. FDA's expectation is that any plans for design space verification be available at the manufacturing site as an element of the change control, validation, and/or knowledge management strategy. Providing data for initial design space verification and a high-level overview of the plan for design space verification over the product lifecycle can be beneficial to the review of the application.

6. What if unexpected results/events are obtained during the design space verification studies?

If the verification studies prove the process does not meet the predefined product quality attributes in a new region of the approved design space, this may indicate an underlying issue with the design space or a flaw in the assessment or verification plan. Changes to the boundaries or description of the design space and any required changes to design space verification protocol should be reported to the Agencies, using appropriate notification categories, in accordance with regional requirements.

Appendix 1 and 2 address regional expectations and regulations

Appendix 1: EU's expectations

7. How can a design space be verified at commercial scale for biological products?

Principles laid down for chemical products are applicable to biological products. In addition, verification studies should provide evidence that the quality attributes of the product are comparable prior to and after the change. This could include a proposal for modular sets of tests and acceptance criteria to be deployed, taking into account the nature of the change and its associated risk.

8. What is the difference between process validation and design space verification?

Design space verification should not be confused with process validation. Both take into consideration prior knowledge and development conclusions and are conducted at commercial scale, however the scope of the studies are not the same. Whereas process validation demonstrates consistency of the process at normal operating ranges, design space verification demonstrates that scale effect and/or model assumptions are under control in the new area of design space and do not affect product quality. Unlike validation which covers all the steps of the manufacturing process, verification studies refer only to those operations where a design space has been proposed. In order to address the risks identified during the risk assessment of operating in the unverified area of the design space the verification studies may also include testing / monitoring of additional parameters or at an increased frequency as compared to the routine control strategy. When verification data proves that the extent of movement within the design space is of high risk (e.g. critical quality attributes are met but close to edge of failure identified at laboratory/pilot scale), process validation (consistency of the process) in the new area of design space (new NOR) should also be considered. A protocol for design space verification should be submitted in section 3.2.R. irrespective of the validation approach. When a strategy for continuous verification is envisaged, where relevant, the elements of design space verification should be included as part of the continuous verification protocol. It is understood that when an applicant can demonstrate that the design space is scale independent then a verification protocol is not requested in the dossier. NB: Continuous Process Verification is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8).

Appendix 2: FDA expectations

9. How should design space verification approach be addressed in the pharmaceutical quality system?

FDA recommends that firms have a written plan for when and how to evaluate the need for design space verification under their pharmaceutical quality system. FDA's expectation is that such plans for design space verification be available at the manufacturing site. Additionally, it can be beneficial to the review of the application for the applicant to include in the initial submission a high-level overview of the plan for design space verification over the product lifecycle.