Annex 3

Considerations for requesting analysis of medicines samples

An earlier version of this guidance was published as *Considerations for requesting analysis of drug samples* in 2002.[1]

Medicines quality control testing independent of manufacturers is an important tool of medicines regulation. However, it demands considerable resources and the need for analysis should therefore always be thoroughly considered. Independent quality control testing should be performed if it adds value to the evaluation performed, when viewed from a public health perspective, and it should not cause unnecessary delays in access to medicines.

Testing should focus on medicines most likely to pose a risk to patients, for example, medicines:

- produced by manufacturers for which poor evidence of compliance with the principles of good manufacturing practices (GMP) (*1*) is available, or where the origin is uncertain;
- suspected of being falsified;
- suspected of being substandard because of incorrect distribution or storage conditions, or their instability;
- suspected of causing adverse reactions due to a quality defect;
- for which analytical testing results are needed as evidence in litigation (requires the implementation of a rigorous chain of custody – see World Health Organization (WHO) guidelines) (*2*).

The risk of poor quality should be assessed before deciding to request analysis of a particular product. For example, if the manufacturing site has been found to comply with GMP principles, the manufacturer is under regular supervision of an authority applying international standards, and there is no specific reason for testing of the product (such as a quality complaint or a suspicion of quality deterioration during distribution or storage), the manufacturer's batch certificate may be relied upon to indicate the quality of the product. Such a certificate should be issued in accordance with the criteria applicable to the WHO Model Certificate of good manufacturing practices (*3*) or WHO Certification Scheme (*4*).

[1] This guidance was previously published as Annex 4 in the WHO Technical Report Series, No. 902, 2002.

Independent post-production testing may be performed by regulators for different reasons and in various regulatory phases of the medicine's life. The following should be borne in mind when considering testing approaches:

- pre-registration testing of samples submitted for registration
  - As the sample is selected by the manufacturer, it may not provide a true picture of product quality. Testing at this stage may be useful to assess functionality of analytical methods in local conditions in certain rare cases when data reviewers have some doubts.
- Official batch release of some biological products by the national medicines regulatory authority (NMRA)
  - This is usually requested to fulfil national regulations for specified products and described in guidelines.
- Pre-marketing testing of all or of selected batches
  - Often samples of imported medicines are collected at points of entry into a country. It would be reasonable to subject them to screening and select for testing only those that show physical signs of instability or deterioration (*5*), other indications of inferior quality, or those whose origin is suspicious. Routine testing of each imported batch is not considered reasonable as the quality of medicines should in principle be assured through the registration process. Batch-to-batch testing may be worthwhile in specific situations, for example, when proper registration assessment and verification of compliance with good practices in production and/or product development is not feasible. Again the risk of poor quality should be assessed before deciding on the testing of a particular product.
- Post-marketing testing as risk-based sampling and surveillance/monitoring projects
  - The advantage of this approach is the selection of samples that are in the distribution chain and are intended for administration to patients. Detailed advice is provided in WHO *Guidelines on the conduct of surveys of the quality of medicines* (*6*).

1. Selection of tests and specifications

Tests to be performed and applicable specifications depend on the reasons for testing a particular sample. Full-scale testing is expensive and it may be reasonable to limit the tests chosen to those that can provide the answers sought. However, tests should always be considered in terms of logical combinations: for example, a

dissolution test or a test for impurities without assay/potency, would not provide sufficient information.

Selection of specifications (methods and limits) for testing again depends on the reasons for testing a particular sample. If the compliance of a product with registered specifications is to be verified, specifications approved by the NMRA as part of the registration process should be used.

If products containing the same active pharmaceutical ingredients in the same dosage form produced by different manufacturers are to be compared, pharmacopoeial specifications should be used. However, noncompliance with pharmacopoeial specifications may not necessarily imply noncompliance of the test product with the registered specifications. Also, in spite of efforts to harmonize pharmacopoeias, there are still many differences between them. When a monograph for a particular medicine is available in more than one pharmacopoeia the ability of the respective specifications to reveal quality problems should be considered and the monograph selected accordingly. In particular, when impurities are evaluated, the suitability of the pharmacopoeial monograph tests for the detection of impurities should be evaluated, especially if the product is from a new source, which may cause it to have a different impurity profile.

If samples suspected of being falsified are to be tested, manufacturers' or pharmacopoeial methods may not be sufficient and further examination should be conducted (for guidance on such investigation see WHO guidelines (*2*)).

If necessary, advice on selection of tests and specifications should be sought from an experienced laboratory.

2. Selection of laboratory and communication before samples are submitted

Once it has been decided to test a medicine, a laboratory, which produces reliable testing results and is capable of and competent to perform the tests required, should be selected. This can be a local national laboratory or a contracted laboratory in the same or in another country.

In general, to demonstrate that testing results are reliable, a laboratory should work in compliance with internationally recognized standards such as *WHO good practices for pharmaceutical quality control laboratories* (*7*) or ISO 17025 (*8*). Compliance with the relevant standard should be verified, for example, the laboratory should be WHO-prequalified,[2] or ISO 17025 accredited by an internationally recognized accreditation body. Assurance that the laboratory

[2] The list of WHO-prequalified laboratories can be found at www.who.int/prequal.

works in a reliable manner can also be obtained by organizing an audit by competent auditors or using the audit report from an independent third party, if available.

Before submitting samples to a laboratory, an understanding of its capability to carry out the requested tests and an agreement on performance of the analysis should be reached. The following information, as a minimum, should be provided to the laboratory:

- the reason(s) for the request and the purpose of the analysis;
- the composition of the product(s) (using International Nonproprietary Names (INNs), where possible), concentration or strength and pharmaceutical dosage form;
- a reference to specifications, including (if needed) analytical methods that should be used;
- the expiry date(s) of the sample(s), required storage conditions and duration of the storage of retention samples;
- the number of samples of each product to be tested;
- the date by which testing results are expected;
- the proposed mode of payment for the analysis;
- the preferred language and format of the report containing the results, and the method to be used to transmit the results.

The laboratory that has been contacted should indicate, as quickly as possible, whether or not it is able and willing to undertake the analysis. Any laboratory has the right to decline a request for analysis without furnishing any explanation.

If the laboratory agrees to undertake the analysis, the following should be communicated to the requesting party and mutually agreed:

- the size of the sample (minimum number of dosage units) required for each product (if possible, the number should be sufficient for conducting the tests; investigation and confirmatory testing for those found to be out of specification; and retention of samples to be used in case of dispute);
- any additional tests that may be required or recommended;
- the cost and the mode of payment;
- a tentative estimate of how long the analysis will take.

It is recommended that an appropriate arrangement between the requesting party and the laboratory that will perform the tests should be formalized. The arrangement should, in addition to the points above, settle issues such as liability, confidentiality, acceptance of a possible audit of the laboratory, deadlines, retention period for samples and records, and access to records and retained

samples. The arrangement should also specify when the testing results need to be communicated rapidly (such as when defects that can endanger patients' health are identified). The responsibilities of the two parties should be defined.

An example of an analysis request form is shown in Appendix 1.

3. Submission of samples

Upon reaching agreement with a laboratory, the sample(s) should be dispatched by the requesting party. If samples are not delivered to the laboratory directly by the requesting party, they should be transported using a courier service to avoid any delays and deterioration of the quality. Unless there are special circumstances, the sample(s) must be kept in the original packaging and suitably packaged and labelled to avoid breakage and contamination during transport (*9*). Freezing should be avoided during air transport and, where required, the cold chain should be maintained. When transporting temperature-sensitive medicines, temperature data loggers may be included within shipments to document that appropriate temperatures have been maintained during prolonged transit.

When sending samples to another country, delays in customs clearance should be prevented. The accompanying documents should state that the samples are being sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market. In the case of products that are subject to legal controls on exportation, appropriate arrangements must be made by the requesting party to ensure due compliance with customs requirements. The laboratory may be able to advise on further precautions. If the country where the laboratory is located requires permission for importation of samples, the laboratory may assist in applying for permission, to avoid long clearance procedures. The laboratory should be informed of the dispatch of the shipment, including the tracking number as provided by the courier service, to enable it to follow the shipment and arrange for prompt collection.

If the product to be tested contains a controlled substance (a substance regulated under the international drug control conventions[3]) the requirements of the relevant national legislation (for example, secure storage, documentation, etc.), are to be implemented.

As soon as the sample has been received by the laboratory, the requesting party should be notified of the delivery and condition of the sample. This information can assist any investigations at a later stage.

[3] http://www.incb.org/incb/en/narcotic-drugs/1961_Convention.html; http://www.incb.org/incb/en/psychotropic-substances/1971_convention.html; http://www.incb.org/incb/en/precursors/precursors/legislation_and_control/legislation_and_control.html.

4. Analytical results

All analyses undertaken by a laboratory should be performed in accordance with the specifications mentioned in the request for analysis, or as subsequently agreed, and conducted in compliance with *WHO good practices for pharmaceutical quality control laboratories* (*7*). All individual results (all test data), with acceptance criteria should be reported (*7*). The results should be compiled in the agreed language in the form of an analytical test report or certificates of analysis in line with WHO guidelines (*7*, *10*) and transmitted by the agreed method.

References

1. WHO good manufacturing practices for pharmaceutical products. Geneva, World Health Organization, http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/ accessed 30 October 2017).
2. WHO guidance on testing of "suspect" falsified medicines In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 5 (WHO Technical Report Series, No. 1010).
3. WHO Model Certificate of good manufacturing practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-seventh report. Geneva: World Health Organization; 2003: Annex 5 (WHO Technical Report Series, No. 908).
4. Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fourth report. Geneva: World Health Organization; 1996: Annex 10 (WHO Technical Report Series, No. 863).
5. The International Pharmacopoeia, sixth edition. Quality specifications for pharmaceutical substances and dosage forms together with supporting general methods for analysis. Geneva: World Health Organization; 2016 (http://who.who.int/phint/).
6. Guidelines on the conduct of surveys of the quality of medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 7 (WHO Technical Report Series, No. 996).
7. Good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957).
8. General requirements for the competence of testing and calibration laboratories. Geneva: International Organization for Standardization; 2005 (ISO/IEC 17025).
9. WHO guidelines for sampling of pharmaceutical products and related materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. Geneva: World Health Organization; 2005: Annex 4 (WHO Technical Report Series, No. 929).
10. Model certificate of analysis. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 4 (WHO Technical Report Series, No. 1010).

Appendix 1

Example of an analysis request form

Requesting party	
Name, address	
Contact person: name, phone no., email	

Product to be tested[a]	
Name, dosage form	
INN(s), strength	
Package size, type and material of the container	
Name and address of the manufacturer	
Number of samples to be tested	
Batch number/s	
Date/s of manufacture	
Date/s of expiry	
Required storage conditions	
Sample/s source	
Sample size: number of dosage units/packages per sample[b]	
Testing	
Reason/s for the request and purpose of the analysis	
Reference to specifications (pharmacopoeial monograph or methods and specifications attached to the request)	

Table *continued*

Tests requested – tick ✓ requested tests			
Identity		Specific optical rotation	
Assay		Melting range/point	
Related substances/impurities		Conductivity	
Dissolution		Refractive index	
Disintegration		Microbial enumeration tests	
Friability		Tests for specified microorganisms	
Fineness of dispersion		Sterility	
Uniformity of dosage units		Bacterial endotoxins	
Water content		Other tests (please specify):	
pH value			
Relative density			
Viscosity			
Date by which testing results are expected			
Period for which retention samples should be kept			
Preferred language and format for reporting results			
Method to be used for transmission of the results			

[a] Section to be repeated for each product tested.

[b] To be agreed with the laboratory.

Signature of the person representing the requesting party
Name, function

Date