Guidance for Industry

Drug Substance

Chemistry, Manufacturing, and Controls Information

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Review (CBER)
Center for Veterinary Medicine (CVM)

January 2004
CMC

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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TABLE OF CONTENTS[1]

[1] Alphanumeric designations in parentheses that follow headings show where information should be placed in applications that are submitted in Common Technical Document (CTD) format.

GUIDANCE FOR INDUSTRY[2]

Drug Substance
Chemistry, Manufacturing, and Controls Information

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale and/or justification for the proposed revision.*
- *Identify specific comments by line numbers; use the pdf version of the document whenever possible.*
- *If possible, e-mail an electronic copy (Word) of the comments you have submitted to the docket to* cummingsd@cder.fda.gov.

I. INTRODUCTION

Information on the chemistry, manufacturing, and controls (CMC) for the drug substance must be submitted to support the approval of original new drug applications (NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), and abbreviated new animal drug applications (ANADAs).[3] This guidance provides recommendations on the CMC information for drug substances that should be submitted to support these applications. The guidance is structured to facilitate the preparation of applications submitted in Common Technical Document (CTD) format.

This guidance addresses the information to be submitted for drug substances to ensure continued drug substance and drug product quality (i.e., the identity, strength, quality, purity, and potency).

[2] This guidance has been prepared by Drug Substance Technical Subcommittee of the Chemistry Manufacturing and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluations and Research (CBER) and the Center for Veterinary Medicine (CVM) at the FDA.

[3] See 21 CFR 314.50(d)(1) and 514.1(b)

This guidance provides recommendations on the information that should be included for the following topics:

- Nomenclature, structure, and general drug substance properties
- Manufacture
- Characterization
- Control of drug substance
- Reference standards or materials
- Container closure system
- Stability

The recommendations provided in this guidance apply to the following types of drug substances:

- Drug substances manufactured by chemical synthesis
- Highly purified and well characterized drug substances derived from plants or animals [4]
- Semisynthetic drug substances manufactured by the chemical modification of a highly purified and well characterized intermediate derived from plants or animals
- The synthetic portion of the manufacturing process for semisynthetic drug substances manufactured by the chemical modification of an intermediate produced by conventional fermentation.

The guidance does not provide specific recommendations relating to the following:

- Monoclonal antibodies
- Peptides
- Oligonucleotides
- Radiopharmaceuticals
- Medical gases
- Drug substances that are not well characterized (e.g., botanicals, some proteins) derived from plants or animals
- Drug substances derived using transgenic technology
- Drug substances derived directly from or manufacturing operations involving fermentation (conventional fermentation or using rDNA technology) or tissue or cell culture.

More detailed guidance on the content of an application may be available in separate guidance documents for specific types of drug substances (see section II.C). Applicants with drug substances not specifically covered by this (*Drug Substance* guidance) or another guidance can apply the content recommendations in this guidance, as scientifically appropriate, and/or can contact the appropriate chemistry review teams for guidance.

[4] For purposes of this guidance, d*rug substances derived from plants or animals* does not include materials produced by plant cell fermentation, animal cell or tissue culture, or through use of transgenic technology (e.g., biotechnology-derived protein drug products).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

This guidance, when finalized, will replace the guidance entitled *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (February 1987).

II. BACKGROUND

A. The Common Technical Document — Quality (CTD-Q) Format

In November 2000, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued harmonized guidance for the format of drug product applications (i.e., Common Technical Document (CTD)). The CTD describes a format for applications that (supplemented with regional information) can be used for submission to the regulatory authorities in the United States, European Union, and Japan. One focus of this effort was harmonizing the format for quality information (i.e., chemistry, manufacturing, and controls) that will be submitted in an application. FDA's guidance on *M4Q: The CTD — Quality* describes the format for the quality information submitted in Module 3 of an application and provides additional information on formatting aspects of an application. Applicants can submit NDAs, ANDAs, NADAs, and ANADAs using the CTD-Q format.[5] Applicants should review FDA's guidance on *M4Q: The CTD — Quality* and other related CTD guidance documents for detailed formatting recommendations on preparing an application in CTD format.

Module 3 of each NDA and ANDA should include the specified CTD sections: Drug Substance (3.2.S), Drug Product (3.2.P), Appendices (3.2.A), Regional Information (3.2.R), and Literature References (3.3). In some cases, the majority of information to address the drug substance sections will be incorporated by reference from a master file (see section II.D.2). However, an applicant should still provide information to address some of the drug substance subsections. Recommendations on the content of the drug product section (3.2.P) of Module 3 will be the provided in the guidance *Drug Product — Chemistry, Manufacturing, and Controls Information* (*Drug Product* guidance), when finalized.[6] The Appendices, Regional Information, and Literature References sections include information for both drug substance and drug product, as appropriate.

[5] The information in animal drug applications is commonly presented in the order of the required CMC information specified under section § 514.1(b)(4) and (5). Although the CTD-Q format was developed for human drugs, the drug substance information to support NADAs and ANADAs can be formatted according to the CTD-Q format or any alternative format that provides the appropriate information to support the application.

[6] A draft version of this guidance published on January 28, 2003 (68 FR 4219).

This *Drug Substance* guidance has been organized in a format conforming to Module 3 of the CTD, and it provides CMC content recommendations specific to drug substance, including recommendations for the Appendices, Regional Information, and Literature References sections. Alphanumeric designations in parentheses corresponding to the CTD format follow relevant headings and text to show where information is to be placed in the CTD.[7] Recommendations specific to drug product, including recommendations for the Appendices, Regional Information and Literature References sections, will be provided in the *Drug Product* guidance.

- Multiple Drug Substances in an Application

When an application is submitted for a drug product involving two or more drug substances (e.g., combination drug product, copackaged drug products), information for each drug substance should be presented separately in the application. Information presented separately means one complete S section for one drug substance followed by other complete S sections for additional drug substances. All of the information pertinent to each one of the drug substances (general information, manufacture, characterization, control, standards, container closure system, and stability) should be provided in a single section.

B. Content of an Application

The application should include information in every S subsection for each of the drug substances and manufacturing schemes (e.g., alternative processes, manufacturing site) intended for approval under the application. Information should be provided in the Appendices, Regional Information, and Literature References sections for each of the drug substances and manufacturing schemes, as appropriate. If an Appendices or Regional Information subsection or the Literature References section is not applicable, this should be stated in the application.

C. Additional Guidance

This *Drug Substance* guidance and the *Drug Product* guidance, when finalized, will be the primary *content* guidances for NDA and ANDA applicants. For quality, the general *format* guidance is *M4Q: The CTD — Quality*. These are the first guidances an applicant should consider when preparing the quality section (i.e., chemistry, manufacturing, and controls) of an NDA or ANDA (Module 3).

This guidance references ICH guidance documents cited in the CTD-Q and FDA's guidances on general technical topics (i.e., stability, container closure systems, analytical procedures and methods validation, sterilization process validation, drug master files, and

[7] Arabic numbers have been assigned to specific sections of the CTD. For example, the designation 3.2 before S, P, A, and R indicates Module 3, Body of Data section 2. Where this guidance discusses Module 3, Body of Data section 2, for brevity, the initial designation 3.2 is not repeated throughout the rest of the guidance (e.g., 3.2.S.1.3 reads S.1.3).

environmental assessments) rather than incorporating this detailed information. These guidances are referenced in the text and/or listed at the end of a section. An applicant should refer to these guidances for recommendations on the detailed information that should be included in the application to address the general technical topic.

Finally, an applicant should consider guidances that are available for specific technical issues or type (e.g., synthetic peptides) of drug substance when preparing its application. These guidances provide additional recommendations on unique scientific and technical aspects of the topic. Some references to these types of guidances are included in this guidance. However, the references are given only as examples, and the list is not meant to be all-inclusive. Some examples of these types of guidance include the following:

- *Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances*
- *Submission of Chemistry, Manufacturing and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use*, CBER/CDER (under development)
- *Botanical Drug Products* (under development)
- *Fermentation Derived Drug Substances and Intermediates and Associated Drug Products* (under development)
- *Synthetic Oligonucleotides; Submission of Chemistry, Manufacturing, and Controls Information* (under development)
- *Radiopharmaceutical Drug Products: Chemistry, Manufacturing and Controls Information* (under development)

FDA continues to update existing and publish new guidance documents. An applicant should use current guidance when preparing an NDA, ANDA, NADA or ANADA submission.[8]

D. References to Other Applications or Master Files (MFs)

1. Other Applications

In some cases, chemistry, manufacturing, and controls information about drug substances is provided in one application by reference to pertinent information in another application. This situation is less common than inclusion of information by reference to a MF and usually occurs when the same firm submits both applications.

An applicant must identify in the application all other referenced applications, and each reference to information submitted in another application must identify where the information can be found in the referenced application (21 CFR 314.50(a)(1) and 514.1(a)). If the referenced application was submitted by a firm other than the applicant, the referencing application must contain a written statement that authorizes the reference,

[8] Current guidance documents are available on the Internet at http://www.fda.gov/cder/guidance/index.htm, http://www.fda.gov/cber/guidelines.htm, and http://www.fda.gov/cvm/guidance/published.htm.

signed by the holder of the referenced application (21 CFR 314.50(g)(1), 314.420(b). and 514.1(a)).[9] Copies of letters of authorization (LOAs) should be submitted in Module 1 of the NDA or ANDA or in the appropriate section of an NADA or ANADA.

2. Master Files (MFs)

This guidance describes chemistry, manufacturing, and controls information for drug substances that should be submitted to the Agency as part of the process of seeking the approval of an NDA, ANDA, NADA, or ANADA. When a drug substance is manufactured by a firm other than the applicant, much of this information is frequently provided by reference to one or more Type II MFs rather than directly in an application. The CMC information in a Type II MF can be organized in CTD-Q format. Under FDA's regulations, an application can incorporate by reference all or part of the contents of any MF to address particular drug substance issues if the MF holder provides written authorization (i.e., LOA) to the applicant and the authorization is included in the application (Module 1 for an NDA or ANDA or in the appropriate section of an NADA or ANADA). The authorization must specifically identify the material being incorporated by reference (21 CFR 314.420 and 514.1(a)). The incorporated material should be identified by name, reference number, volume and page number of the MF, and date of submission. See 21 CFR 314.420, CDER's guidance on *Drug Master Files,* and CVM's guidance on *Preparation and Submission of Veterinary Master Files* for more information.

Both the applicant and the drug substance manufacturer (MF holder) contribute to establishing and maintaining the identity, strength, quality, purity, and potency of the applicant's drug products by manufacturing and controlling the drug substance in accordance with the information submitted in the application and, by reference, in the MF. The following recommendations pertain to location of information in the MF and/or application when an applicant and Type II MF holder are different firms.

- **General Information (S.1[10]):** Both the MF and the application should include this information. These sections should contain similar, though not necessarily identical, information. For example, if an applicant performed screening studies and established the existence of multiple polymorphs, information concerning these polymorphs might be present in the application but not in the MF.

- **Manufacture (S.2):** The application should identify in S.2.1 the manufacturers of each drug substance with appropriate administrative information (see section IV.A). The MF should include this information for its manufacturing operations and any

[9] CVM discourages the reference of NDAs or ANDAs for drug substance information. In these instances, CVM recommends that the drug substance information be included in a master file or incorporated in the applicant's NADA or ANADA.

[10] Alphanumeric designations in parentheses that follow headings show where information should be placed in applications that are submitted in Common Technical Document (CTD) format.

contract facilities that are used (e.g., intermediate manufacturers, laboratories). In general, a MF can be referenced for the information recommended in S.2.2 through S.2.6. However, the information should be augmented by the applicant, as appropriate. For example, if the applicant micronizes drug substance purchased from a MF holder the information on the micronization process should be included in the application.

- **Characterization (S.3**): In general, a MF can be referenced for this information. However, the information should be augmented by the applicant, as appropriate. For example, characterization information on physical properties critical to the applicant's product, such as solid state form or particle size distribution, should be included in S.3.1 by the applicant under certain circumstances (e.g., applicant manipulates the physical property (micronizes), the MF holder has not characterized the physical property). Furthermore, information on an applicant's studies to characterize impurities (S.3.2) can be warranted to support the applicant's drug substance controls.

- **Control of Drug Substance (S.4):** In general, information recommended in S.4 should be provided in both the MF and the application. However, reference to an MF can be appropriate for some of the information in S.4.2 through S.4.5 if the MF holder and applicant are working together to develop the drug substance controls. Both the MF and the application should include a drug substance specification (S.4.1). The MF could include more than one drug substance specification if the holder sells different technical grades of the drug substance (e.g., micronized and nonmicronized).

- **Reference Standards (S.5):** In general, information should be provided in both the MF and the application. However, reference to a MF can be appropriate for some of the information if the MF holder and applicant are working together to develop the reference standard.

- **Container Closure System (S.6):** In general, MFs can be referenced for this information. However, the information should be augmented by the applicant, as appropriate.

- **Stability (S.7):** In general, MFs can be referenced for this information. However, the information should be augmented by the applicant, as appropriate. For example, an applicant might perform stress studies to support the analytical procedures it used to control the drug substance.

- **Appendices (A):** In general, MFs can be referenced for this information. However, the information should be augmented by the applicant, as appropriate.

- **Regional Information (R):** Comparability protocols can be included in both the MF and application (R.2.S). A methods validation package should be included in the application (R.3.S).

- **Literature References (3.3):** Both the MF and the application should include literature references as warranted.

Type II MFs for drug substance intermediates can also be submitted in the CTD-Q format. However, not all sections of the CTD-Q format would apply (e.g., S.4). The CMC information provided to support an intermediate should be appropriate for the particular situation (e.g., process, complexity of the molecule).

III. GENERAL INFORMATION (S.1)

General information on the nomenclature, structure, and general properties of the drug substance, should be provided in S.1.

A. Nomenclature (S.1.1)

All appropriate names or designations for the drug substance should be provided in S.1.1. Any codes, abbreviations, or nicknames used in the application to identify the drug substance should also be listed, including the following, if they exist or have been proposed. A name that has not yet been finalized should be identified as proposed in the list.

- United States Adopted Name (USAN)
- Compendial name [11]
- Chemical names (e.g., Chemical Abstracts Service (CAS), International Union of Pure and Applied Chemistry (IUPAC))
- Company names or laboratory codes
- Other nonproprietary names (e.g., International Nonproprietary Name (INN), British Approved Name (BAN), Japanese Accepted Name (JAN))
- Chemical Abstracts Service (CAS) Registry Number

B. Structure (S.1.2)

Information on the chemical structure of the drug substance should be provided in S.1.2. This information should include:

- one or more drawings to show the overall chemical structure of the drug substance, including stereochemistry
- molecular formula
- molecular weight

[11] A compendial name is a name that appears in an official compendium as defined in the Federal Food, Drug, and Cosmetic Act (e.g., United States Pharmacopeia (USP)) (§ 201(j) (21 U.S.C. 32(i)).

For a naturally derived protein drug substance, the information should include:

- the schematic amino acid sequence indicating glycosylation sites or other posttranslational modifications
- a general description of the molecule (e.g., shape, disulfide bonds, subunit composition)
- number of amino acid residues
- molecular weight

C. General Properties (S.1.3)

A list should be provided of the general physicochemical properties of the drug substance. Other relevant properties of the drug substance should also be listed. Relevant properties are those physical, chemical, biological and microbiological attributes relating to the identity, strength, quality, purity, and/or potency of the drug substance and, as appropriate, drug product. The information should include, as appropriate:

- A general description (e.g., appearance, color, physical state)
- Melting or boiling points
- Optical rotation
- Solubility profile (aqueous and nonaqueous, as applicable)
- Solution pH
- Partition coefficients
- Dissociation constants
- Identification of the physical form (e.g., polymorph, solvate, or hydrate) that will be used in the manufacture of the drug product
- Biological activities

For a naturally derived protein drug substance, additional information should be included, such as:

- Isoelectric point
- Extinction coefficient
- Any unique spectral characteristics

If the drug substance can exist in more than one physical form, the information included in S.1.3 should be for the form (or forms) of the drug substance that will be used in the manufacture of the drug product. Detailed information on the characterization (e.g., X-ray powder diffraction data, thermal analysis curves) of these and other physical forms and conditions required to produce one form or another should be provided in S.3.1.

Additional guidance is available in:

- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

IV. MANUFACTURE (S.2)

Information concerning the manufacture of the drug substance, as described below, should be provided in S.2.

A. Manufacturers (S.2.1)

The name, address, and manufacturing responsibility should be provided for each firm (including contract manufacturers and testing laboratories) and each site (i.e., facility) that will be involved in the manufacturing or testing of the drug substance. Each site should be identified by the street address, city, state, and, when available, the drug establishment registration number.[12] The addresses should be for the location where the relevant manufacturing or testing operation will be performed. Addresses for corporate headquarters or offices need not be provided. Building numbers or other specific identifying information should be provided for multifacility campuses. For sites processing sterile drug substances, the sterile processing area (e.g., room) should also be included. Addresses for foreign sites should be provided in comparable detail, and the name, address, and phone number of the U.S. agent for each foreign drug establishment, as required under 21 CFR 207.40(c), should be included.

To facilitate preapproval inspection related activities, it is recommended that the name, telephone number, fax number and e-mail address of a contact person be provided for each site listed in the application. Facilities should be ready for inspection when the application is submitted to FDA.

B. Description of Manufacturing Process and Process Controls (S.2.2)

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. A flow diagram and a complete description of the processes and process controls that will be used to manufacture the drug substance or derive it from a biological source should be provided in S.2.2. If

[12] See 21 CFR part 207 for registration requirements for producers of drugs. The registration number is the seven-digit central file number (CFN) or ten-digit FDA Establishment Identifier (FEI).

alternative processes are to be used, the information should be provided for each alternative. If justification for an alternative process is warranted, the information should be included in S.2.2 (e.g., comparative impurity data on intermediates) or can be cross-referenced if provided elsewhere in the application (e.g., S.4.4).

1. Flow Diagram[13]

A flow diagram that gives the steps of the process and shows where materials enter the process should be provided. The entire manufacturing process should be depicted (i.e., starting materials through drug substance release testing). See Attachments 1 and 2 for information on starting materials. The flow diagram can be supplemented with information presented in tabular form, if appropriate. The flow diagram should include:

- Each manufacturing step with identification of those steps that are critical. These manufacturing steps can include reaction, workup (e.g., extraction), isolation (e.g., centrifugation, distillation), purification (e.g., chromatography, electrophoresis), processing (e.g., micronization), drug substance release testing.
- The name or code number of the material being processed in each manufacturing step, as appropriate
- Chemical structure (including stereochemical configuration where applicable) or biological identification of starting materials, intermediates, structurally complex reagents, postsynthesis materials, and the drug substance
- Molecular formula and molecular weight of chemical starting materials, intermediates, postsynthesis materials, and drug substance
- Solvents, reagents, and auxiliary materials used in each manufacturing step
- Critical process controls and the points at which they are conducted
- Operating parameters (e.g., temperature, pH, pressure) for each manufacturing step
- An indication of whether intermediates are used in situ or isolated before being used in the next reaction step and which intermediates are considered the final intermediates
- Expected yield (percent) for each reaction step

Reagents and other materials should not be identified using only trade (i.e., proprietary) names. If a reaction results in a mixture of products (e.g., two or more isomers), each

[13] Headings that are not followed by alphanumeric designations (i.e., non-CTD-Q headings) are included in this document for ease of providing recommendations on the information that should be included under a CTD-Q heading (in this instance *Description of Manufacturing Process and Process Controls (S.2.2*)). An application submitted in CTD-Q format need not include these non-CTD-Q headings. An applicant can physically or electronically separate information under a CTD-Q heading as it chooses. However, once a particular approach is adopted, the same approach should be used throughout the life of the application.

component of the mixture should be indicated in the flow diagram. However, information on side products and impurities should be provided in S.3.2 (see sectionV.B).

2. Description of the Manufacturing Process and Process Controls

A narrative description of the manufacturing process that represents the sequence of manufacturing steps undertaken and the scale of production should be provided. This description should provide more detail than that given in the flow diagram. The description should identify all process controls and the associated numeric ranges, limits, or acceptance criteria. Furthermore, any process controls that are considered critical process controls should be highlighted. See below for additional information on process controls. The detailed description of the manufacturing process and process controls should include:

- A detailed description of each manufacturing step
- Starting materials or intermediate used in each step, with chemical or biological names and quantities specified
- Solvents, reagents, and auxiliary materials used in each step, with chemical or biological names and quantities specified
- Type of equipment (e.g., Centrifuge) used, including materials of construction when critical
- Identification of the manufacturing steps that are considered critical
- All process controls and their associated numeric ranges, limits, or acceptance criteria, with critical process controls highlighted
- Type of analytical procedure (e.g., HPLC) used for each process test
- Identification of intermediates, postsynthesis materials, and unfinished drug substance that are tested (details should be provided in S.2.4)
- Identification of manufacturing steps that involve recycling of filtrates (mother liquors) to recover reactants, intermediates, or drug substance, including for the purpose of producing or isolating additional crystals (i.e., Second crops) and the process controls on such operation (see section IV.B.3.c)
- Identification of manufacturing steps that use recovered solvents or auxiliary materials (see section IV.B.3.c)
- Identification of manufacturing steps that involve fraction collection (e.g., Chromatographic purification), the process controls on such operations, and the disposition of unused fractions (e.g., Recycling)
- Identification of processes that involve combining intermediate or drug substance batches, drug substance and a diluent, or two or more drug substances
- Yield ranges (weight and percent) for each manufacturing step

Moreover for drug substance derived from a biological source or a semisynthetic drug substance, the description should include information on the processing operations conducted on the biological starting material and other procedures such as:

- Storage and transportation conditions for biological starting materials
- Preparation procedures (e.g., cleaning, drying)
- Isolation processes (e.g., grinding, cell lysis, extraction from biomass)
- Holding times and storage conditions during manufacture
- Procedures used to maintain traceability of all intermediate and drug substance batches back to the batches of the starting material

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in Appendix A.2 of the application when appropriate (see section X.B of this guidance). A statement should be provided that bovine-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are not used or manipulated in the same facility. Submission of additional facility information could be warranted for multi-use facilities where there is a potential for cross-contamination with adventitious agents (see sections X.A and X.B). Additional facilities information for drug substances derived from biological sources should be included in A.1, when appropriate.

Differences between the manufacturing process described in S.2.2 and the manufacturing process used to produce the primary stability batches should be discussed in S.2.6. (see section IV.F).

- **Process Controls**

Process controls is an all-inclusive term used to describe the controls used during production to monitor and, if appropriate, adjust the process and/or to ensure that an intermediate, postsynthesis material, or unfinished drug substance with an established specification or the drug substance will conform to its respective specification. The term includes:

- Operating parameters — conditions that can be adjusted to control the manufacturing process (e.g., temperature, pH, time, mixing speed)
- Environmental controls — conditions associated with the manufacturing facility (e.g., temperature, humidity, clean room classification)
- Process tests — measures used to monitor and assess the performance of an on-going manufacturing operation (e.g., analysis to determine concentration of reactant or product, measuring hydrogen gas uptake during hydrogenation)

- In-process material tests — measures used to assess the quality attributes and/or the suitability for use in the manufacturing process of an isolated intermediate, postsynthesis material, or unfinished drug substance

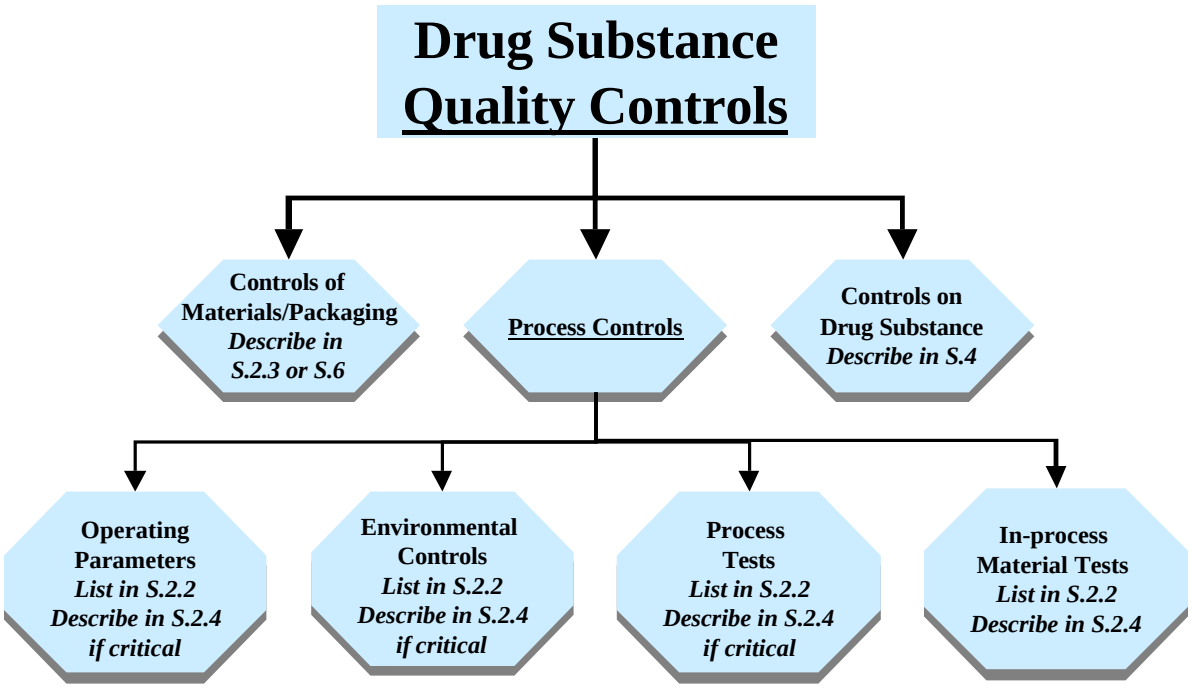
Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. Process tests and in-process material tests can be performed on-line, at-line, or off-line. All process controls, critical or otherwise, should be included in the description of the manufacturing process.

Depending on the drug substance and the manufacturing process, a particular process control may or may not be critical as illustrated in the following examples:

- A mixing speed or temperature can be critical for manufacturing steps for protein drug substances, but may not be critical for similar operations performed on a synthetic chemical
- The humidity to which a powder is exposed during processing can be critical, but may not be critical if the powder is nonhygroscopic
- The clean room classification can be critical for certain steps in the manufacture of a sterile drug substance, but may not be critical for steps before the drug substance is rendered sterile or for a nonsterile drug substance.
- An end-of-reaction test used to determine impurity levels can be critical, but an end-of reaction test to maximize yield may not be critical

All of the operating parameters, environmental conditions, and process tests that ensure each critical manufacturing step is properly controlled should be specifically identified as critical in the flow diagram and description of the manufacturing process in this section of the application (S.2.2) and in S.2.4. All tests on intermediates, postsynthesis materials, and unfinished drug substance should be listed in the description of the manufacturing process in S.2.2 and described in S.2.4. A summary of where information on drug substance quality controls should be located in applications submitted in CTD-Q format is provided in Figure 1.

Figure 1



3. Reprocessing, Reworking, Recycling, Regeneration, and Other Operations

Reprocessing should be described in S.2.2, when appropriate. When used, reworking, recycling, regeneration, and salvaging operations should be described in S.2.2. These operations should be adequately controlled to ensure that there is no adverse effect on the identity, quality, purity, or potency of the drug substance. Moreover, reprocessing and reworking operations should be capable of producing an improvement in one or more quality attributes without having an adverse effect on others. Information (e.g., comparative analytical data) to support the appropriateness of these operations should be included in S.2.2 or can be cross-referenced in S.2.2 if information is provided elsewhere in the application. If the operation involves critical manufacturing steps or intermediates, information should also be provided in S.2.4. However, validation data, when warranted to support the operation, should be provided in S.2.5. (see section IV.E for possible situations when process validation information is warranted.)

a. Reprocessing

Reprocessing is the introduction of an intermediate or drug substance, including one that does not conform to a standard or specification, back into the process and repeating a crystallization or other appropriate chemical or physical manipulations (e.g., distillation, filtration, chromatography, milling) that are part of the approved manufacturing process. See section IV.B.3.e for recommendations on chemical or physical manipulations performed after quality control release of the material.

Continuation of a manufacturing step after a process test has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing. Repetition of a single reaction step should be carefully evaluated with respect to the potential formation of by-products and over-reacted materials. Repetition of multiple reaction steps is considered to be reworking, rather than reprocessing (see section IV.B.3.b).

For most intermediates and drug substances, reprocessing need not be described in the application. In general, the documentation of and data to support the reprocessing of a production batch should be retained by the manufacturer and be available for review by FDA upon request. However, if there is a significant potential for the reprocessing operation to adversely affect the identity, strength, quality, purity, or potency of the drug substance, the reprocessing operations should be described and justified in this section (S.2.2) of the application. For example, CDER would consider reprocessing proteins to be reprocessing operations that should be described in the application.

Reprocessing is considered a nonroutine event. If frequent reprocessing is expected, the procedures should be included as part of the manufacturing process described in the application. Depending on the frequency and type of reprocessing, a reprocessing operation that is included in the application can be (1) specified for use under certain circumstances (e.g., repetition of a purification step when impurities are found at or above a designated level) or (2) incorporated into the existing manufacturing process and performed on each batch when reprocessing occurs for the majority of batches.

b. Reworking

Reworking is subjecting an intermediate or drug substance that does not conform to a standard or specification to one or more manufacturing steps that are different from the manufacturing process described in the application to obtain acceptable quality intermediate or drug substance. Repetition of multiple reaction steps is considered to be reworking because the material to be reintroduced into the process is not similar to the original reactant. Repetition of multiple reaction steps is discouraged because of concerns relating to unexpected impurities and degradants.

Reworking is considered a nonroutine event. In general, reworking operations are developed postapproval, and the application is updated through submission of a prior approval supplement that provides test results and, if appropriate, new or updated analytical procedures that are demonstrated to be appropriate to evaluate the effect of the reworking procedure on the identity, quality, purity, or potency of the drug substance. However, if reworking operations are anticipated at the time of the original submission, they should be described in this section of the application (S.2.2) with justification for the reworking operation.

c. Recovery

The use of recovered solvents and recycling of filtrates (mother liquors) to recover reactants, intermediates, or drugs substance, including for the purpose of producing or isolating additional crystals (i.e., second crops), should be described in S.2.2. Recovery operations should be adequately controlled so impurity levels do not increase over time.

Recovered solvents can be used with or without further processing to improve the quality of the solvent as long as the quality of the recovered solvent is appropriate for its intended use. The use of recovered solvents, including the point at which they might be used in the process, should be included in the description of the manufacturing process. The solvent recovery operation itself need not be described in detail. However, information should be provided on whether (1) any processing is done to improve the quality of the recovered solvent with a brief description of the process (e.g., distillation) and (2) the recovered solvent comes only from the manufacture of this drug substance or can come from other sources. Appropriate specifications for recovered solvents should be included in S.2.3.

Recycling of filtrates should be included in the description of the manufacturing process if these operations are performed. Information should be provided on the maximum number of times material will be recycled and for the process controls for such operations. Data on impurity levels should be provided to justify recycling of filtrates.

d. Regeneration

The regeneration of materials such as column resins and catalysts should be described in S.2.2 if these operations are performed. The process controls for regeneration operations should be provided. Controls on regenerated material can include, for example, a maximum number of times the material will be regenerated and/or tests to determine the continued suitability (e.g., column efficiency) of the material. When appropriate, specifications for regenerated materials should be included in S.2.3

e. Other Operations

The recommendations for reworking apply to (1) recovery of drug substance from drug product or drug product in-process materials or (2) a drug substance, after it has been released by the quality control department, that undergoes processing to bring the material back into conformance with its specification (e.g., purification of aged material to decrease the level of degradation products to conform with the approved acceptance criteria). The recommendations for reworking operations apply irrespective of whether the operation repeats steps that are part of the approved manufacturing process (see section IV.B.3.b).

Additional guidance is available in:

- ICH: *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

C. Control of Materials (S.2.3)

Information on the materials (starting materials, reagents, solvents, auxiliary materials, and diluents) that will be used to manufacture the drug substance or derive it from a biological source, including purification, should be provided in S.2.3. Information indicating where each material is used in the manufacturing process should be provided in the flow diagram and in the narrative description of the manufacturing process (S.2.2).

When appropriate, specific tests and acceptance criteria to control microbial contamination should be included in the specification for materials used to manufacture drug substances. For materials of biological origin, information assessing the risk with respect to potential contamination with adventitious agents should be provided in Appendix A.2 of the application when appropriate (see section X.B).

1. Starting Materials

For application purposes, *starting materials* mark the beginning of the manufacturing process described in an application. The starting material for application purposes can differ from the *active pharmaceutical ingredient (API) starting material,* which marks the point in the manufacturing process from which appropriate GMP should be applied (as defined in ICH Q7A: *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*). In general, the starting material and API starting material should be the same for a synthetic drug substance. However for a drug substance derived from a biological source, the starting material (e.g., plant) and API starting material (e.g., extract) can be different. In this case, information on the biological source (e.g., potential pathogens, herbicides, pesticides) is warranted in the application so FDA can evaluate the suitability of the biological source as a starting material for drug manufacture (see Attachment 2). The recommendations for starting materials provided in this guidance are for application purposes. See ICH Q7A for recommendations on API starting materials.

Starting materials for a synthetic drug substance are chemical compounds of defined molecular structure that contribute to the structure of the drug substance. A proposed starting material for a synthetic drug substance should be chosen so that sufficient information will be available to FDA on the manufacturing process to evaluate the safety and quality of the drug substance. The FDA considers (1) cells; (2) plants, plant parts,

macroscopic fungi, or algae; or (3) animal tissues, organs, or body fluid from which the drug substance is derived to be the starting material for a drug substance derived from a biological source. For semisynthetic processes, information should be provided for the biological source starting material and starting materials of synthetic origin, if there are any.

The following information should be included in the application to support the proposed starting materials:

- A list of proposed starting materials and/or information on plant or animal starting materials
- A flow diagram
- A specification for each starting material
- Justification for the proposed starting materials, when appropriate

More detailed information and recommendations on the information to support proposed starting materials for synthetic drug substances and starting materials of plant or animal origin are included in Attachment 1 and 2, respectively.

2. Reagents, Solvents, and Auxiliary Materials

The following information should be submitted in S.2.3 for reagents, solvents, and other auxiliary materials (e.g., filter aids, decolorizing agents) used in the manufacture of a drug substance. When contamination with viral adventitious agents or transmissible spongiform encephalopathy (TSE) agents is a concern, additional information may be warranted (see section X.A and X.B). Information on the manufacture of certain reagents (e.g., those produced by rDNA technology) may be warranted and when warranted, this information should be included in S.2.3.

a. List of Reagents, Solvents, and Auxiliary Materials

A list of reagents, solvents, and other auxiliary materials used in the manufacture of a drug substance should be provided.

b. Specification

A specification should be provided for each material. The specification sheet should list all tests to which the material will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test. At a minimum, the reference should identify the type of analytical procedure used (e.g., GC, HPLC).

The tests and acceptance criteria in each specification should be appropriate for the kind of material and its intended use, and should be consistent with the quality of the material used to manufacture the batches of drug substance used to

establish the specification for the drug substance (see sections VI.A, VI.D, and VI.E). For example, extensive purity testing of an inorganic base used to adjust pH would not normally be warranted, but testing of enantiomeric purity might be appropriate for an optically active organic acid used in a resolution step.

Water used in the manufacture of drug substances should be of appropriate quality for its intended use.

3. Diluents

Occasionally the drug substance used to manufacture a drug product is dispersed in a diluent (e.g., conjugated estrogens, nitroglycerin). Information on the controls for the diluent (e.g., lactose, dextrose) should be included in S.2.3. The information should be provided at the same level of detail as for a drug product excipient. Recommendations on control of excipients will be provided in section VI of the *Drug Product* guidance, when finalized.

Additional guidance is available in:

- ICH: *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*
- ICH: *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL17 Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products*

D. Controls of Critical Steps and Intermediates (S.2.4)

In this section of the application, all critical operating parameters, environmental controls, process tests and all tests performed on intermediates, postsynthesis materials, and unfinished drug substance should be listed and their associated numeric ranges, limits, or acceptance criteria should be identified. Any of the tests and associated numeric ranges, limits, or acceptance criteria for intermediates, postsynthesis materials, or unfinished drug substance that are judged to be non-critical can be indicated as such. FDA recommends that the noncritical be listed separately from the critical tests to distinguish them from the critical tests that constitute the specification for the intermediate, postsynthesis material, or unfinished drug substance.

For all critical process controls, the associated numeric ranges, limits, or acceptance criteria should be justified and a brief description of the test provided. Any experimental data to support the justification should be included in this section (S.2.4) as well. For critical operating parameters and environmental conditions, numeric ranges, limits, or acceptance criteria typically can be based on the experience gained during the development of the manufacturing process. (See section IV.E for possible exceptions when process validation information is warranted.) Critical process control values from relevant batches (i.e., those for which batch analyses have been provided in S.4.4) should be provided as part of the justification. Additional information should be provided in this section (S.2.4) under the following circumstances.

- **Biological Tests**

Analytical procedures and associated validation information should be provided for biological tests.[14]

- **Tests Used In Lieu of Drug Substance Tests**

In some cases, results from tests performed during the manufacturing process (e.g., process tests, tests on intermediates, postsynthesis materials, or unfinished drug substance) can be used in lieu of testing the drug substance to satisfy a test listed in the drug substance specification. For example, testing to determine the level of a residual solvent on an isolated intermediate may be sufficient to satisfy a test listed in the drug substance specification provided in S.4.1. This approach, however, should be supported with data that demonstrate that test results or drug substance performance characteristics do not undergo an adverse change from the in-process stage to drug substance. These data, along with the analytical procedure and associated validation information, should be provided in S.2.4. Information should be included in the method validation package (R.3.S), as appropriate. When the same analytical procedure is used for both the in-process test and the drug substance test, the acceptance criterion for the in-process test should be identical to or tighter than the acceptance criterion in the drug substance specification. Tests performed in-process in lieu of testing the drug substance should be included in the drug substance specification (S.4.1) and the results of such tests should be included in the batch analysis report (e.g., certificate of analysis)).

- **Intermediates**

When warranted, a specification should be established for an isolated intermediate to ensure that it has appropriate quality attributes for further downstream processing. A specification for an intermediate should usually include testing for assay and impurities. The specification should be provided in S.2.4.

[14] The term *biological tests* includes biological (e.g., animal, cells), biochemical (e.g., enzyme reaction rates), and immunochemical procedures. In this circumstance, procedures from an official compendium to assess pyrogen, bacterial endotoxin, sterility, and microbial levels are excluded from this definition.

For a semisynthetic drug substance, FDA recommends that the following information be provided in S.2.4 for the intermediate used at the beginning of the synthetic operations:

- The chemical name, CAS Registry Number, structure (including amino acid sequence, if appropriate), molecular formula, and molecular weight
- Evidence supporting the chemical structure
- Information concerning impurities
- The proposed specification for the intermediate

Because the intermediate is obtained from a plant or animal, the evaluation of potential impurities should not be limited to structurally related organic compounds, residual solvents, and inorganic impurities. Other potential sources of impurities (e.g., pesticide or herbicide residues in plant-sourced intermediates) should also be considered and discussed. Information concerning the removal or inactivation of adventitious agents in intermediates obtained from animal sources should be provided in Appendix A.2 as appropriate. The need for heavy metals testing should be considered due to the concentration of metals by some plant species.

- **Postsynthesis Materials**

For synthetic or semisynthetic drug substances, a postsynthesis material is a material that appears in the process after the final intermediate and before the drug substance (unfinished drug substance or form of drug substance used to produce the drug product). Postsynthesis materials can differ from the drug substance, for example, in stereochemical identity, solid state form, or either the absence of a counterion or the presence of a counterion different from that in the drug substance. Although firms have sometimes referred to such materials as *intermediates,* these materials do not meet the definition of intermediate and final intermediate provided in this guidance for synthetic or semisynthetic drug substances. If a specification for a postsynthesis material is established, this specification should be included in S.2.4.

There is no distinction between intermediates, final intermediate, and postsynthesis materials for drug substances derived from biological sources. The in-process materials are referred to as intermediates (see discussion above on *intermediates* for guidance).

- **Unfinished drug substance**

Multiple forms (i.e., *technical grades*) of the drug substance may be part of the manufacturing process described in the application. For example, an applicant might purchase a drug substance from an MF holder and then micronize or further purify the drug substance for use in its drug product. If a specification for an unfinished drug substance is established, this specification should be included in S.2.4. The specification for the form of the drug substance used to produce the drug product should be included in S.4.1.

Additional guidance is available in:

- ICH: *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL17 Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products*

E. Process Validation and/or Evaluation (S.2.5)

Validation information relating to the adequacy and efficacy of any sterilization process (e.g., drug substance, packaging components) should be submitted in this section of the application for sterile drug substances. Furthermore, if a step in the manufacturing process is designed to reduce the amount of microbial contamination, such as for certain drug substances derived from biological sources, information to support the appropriateness of the step should be included. Submission of other manufacturing process validation information in the application is not necessary for most drug substances.[15] However, for naturally derived protein drug substances, information concerning the evaluation of purification processes related to the removal of impurities should be provided in this section. When applicable, validation information should be provided for processes used to control adventitious agents. This information should be included in A.2.

Submission of validation information for reprocessing and reworking operations usually is not warranted. However, it can be warranted when the reprocessing or reworking operation is of the type for which process validation information is submitted when routinely performed or when the reprocessing or reworking operations have a significant potential to affect the identity, strength, quality, purity, or potency of the product (e.g., naturally derived protein drug substances).

F. Manufacturing Process Development (S.2.6)

A description of the manufacturing process for the drug substance throughout the various development phases should be provided in S.2.6. The primary focus of this description

[15] All manufacturing processes should be validated. However, in most cases, the validation information is reviewed during facility audits.

should be the relationship between changes in the manufacturing process or manufacturing site and any associated changes in the chemical or physical properties of the drug substance. Manufacturing changes associated with changes in the impurity profiles of intermediates should also be described. Information for early manufacturing processes (i.e., those used prior to the manufacture of drug substance batches for which chemistry, clinical, or toxicity data will be submitted in the application) need not be provided. If in vitro studies (e.g., dissolution) or in vivo studies (e.g., bioequivalence) on the drug product were warranted because of a change in the drug substance manufacturing process, the study results should be summarized,[16] and a cross-reference to the studies (with study numbers) should be provided in S.2.6.

The primary stability batches should be manufactured using the same manufacturing processes (e.g., synthetic route) and procedures and a method of manufacture that simulate the process intended for production batches as described in S.2.2. Section 2.6 of the application should contain a description of any significant differences between the process used to produce the primary stability batches and the process described in S.2.2 (see section IV.B). The description should include an explanation for the differences.

Additional guidance is available in:

- ICH: *Q3A Impurities in New Drug Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL10 Impurities in New Veterinary Drug Substances*

V. CHARACTERIZATION (S.3)

A. Elucidation of Structure and Other Characteristics (S.3.1)

Data and analysis to support the elucidation of the structure and other characteristics of the drug substance should be provided in S.3.1. Summary information relating to these characteristics should be included in S.1.2 and S.1.3. Key physicochemical characteristics of the drug substance that can influence the performance or manufacturability of the drug product should be discussed in P.2.1.1 for NDAs and ANDAs or the appropriate section of the NADA or ANADA.

1. Elucidation of Structure

[16] Here and elsewhere in the guidance when a summary of clinical or nonclinical information is recommended, the summary information or a cross-reference to the appropriate summary information in Module 2 of a CTD formatted NDA or ANDA can be provided in the specified Module 3 section.

The chemical structure of the drug substance should be confirmed using physical and chemical techniques such as elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, infrared (IR) spectroscopy, X-ray crystallography, and other tests (e.g., functional group analysis, derivatization, complex formation). Issues such as counterion stoichiometry, regiochemistry, geometric and configurational isomerism, and absolute stereochemistry should be addressed. When the drug substance consists of more than one molecular species, information confirming the structure of each should be provided. The elucidation of structure of synthetic and semisynthetic drug substances, including stereochemistry, can be supported by the chemical structures of synthetic precursors. The amount of data warranted to support the elucidation of structure can vary depending on the complexity of the molecule.

For naturally derived proteins, the primary, secondary, tertiary and, if applicable, quaternary structures should be confirmed using appropriate techniques such as amino acid compositional analysis, full amino acid sequencing, peptide mapping, and mass spectrometry. Additional tests (e.g., isoforms analysis, carbohydrate composition or sequence) may be warranted for glycoproteins. For naturally derived protein drug substances, additional information on structural characterization can be found in ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.*

2. Physicochemical Characterization

Detailed information on and data to support the physicochemical characterization of the drug substance should be provided in S.3.1. This information should include data to support the general properties listed in S.1.3 (e.g., optical rotation, solubility profile, dissociation constant) as well as information and data on more complex physicochemical properties that are not included in the list of general properties (e.g., heterogeneity of naturally derived proteins). Information can include data from various analytical procedures such as X-ray diffraction (single crystal or powder), thermal analysis (e.g., differential scanning calorimetry, thermal gravimetric analysis, hot-stage microscopy), particle size analysis, or other spectroscopic techniques (e.g. IR, Raman, solid-state NMR, mass). Moreover, for proteins information can include data from techniques such as electrophoresis (e.g., sodium dodecyl sulfate (SDS)-polyacrylamide gel, capillary), isoelectric focusing, optical analysis (e.g., circular dichroism), column chromatography (e.g., size exclusion, reverse phase-HPLC, ion exchange), and Western-blot.

The kind and extent of the physicochemical characterization information that should be provided depends on (1) the type of drug substance (e.g., synthetic molecule, protein), (2) the type of dosage form in which the drug substance will be used, (3) the ability or tendency of the drug substance to occur in one or more solid state forms, and (4) the importance of the differences in physical characteristics of the different forms to the stability, dissolution, or bioavailability of the drug product. The information in S.3.1 can be cited elsewhere in the application, for example, to justify proposed process controls or lack thereof (see section IV.D), or the presence or absence of tests for physical

characterization in the proposed drug substance specification (see sections VI.A and VI.E).[17]

Based on the above stated considerations, an applicant or drug substance manufacturer should investigate whether a drug substance is capable of existing in different solid state forms. Solid state form in this context refers to amorphous and crystalline forms, hydrates, and solvates. The information can include studies of (1) the conditions that lead to the formation of one or another solid state form or (2) the conditions under which one solid state form can be converted or equilibrated with another. Applicants do not need to investigate the occurrence of different forms under conditions that deviate significantly from the conditions used in the manufacturing processes for the drug substance and drug product. However, screening a variety of solvents with different polarities and hydrogen-bonding properties can be valuable for early detection of other polymorphs.
At an appropriate stage of development, the potential for interconversion of solid state forms should usually be investigated in stability studies. A summary of these investigations should be included in S.3.1 of the application even if no other forms were found. Information on differences in particle size distribution or crystal habit (shape) can also be important in some circumstances.

In some cases, characterization of the drug substance will be insufficient to conclude whether the physical properties of the drug substance will have an impact on the dissolution or bioavailability of the drug product, and further studies on the drug product itself should be conducted. A summary of these studies should be provided in section P.2.1.1 of the NDA or ANDA or the appropriate section of the NADA or ANADA.

3. Biological and Other Relevant Characteristics

Information on the elucidation of other relevant characteristics should be provided as appropriate. For example, information on biological activity, purity (e.g., product-related substances), and when appropriate, immunochemical properties should be provided for naturally derived protein drug substances.

Additional guidance is available in:

- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

[17] ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* provides guidance on how to decide what controls on solid state form or particle size are appropriate. Although this guidance applies only to new drug substances of synthetic chemical origin, the same principles for evaluating solid state form can be used, when appropriate, for other types of drug substances.

B. Impurities (S.3.2)

Information on drug substance impurities should be provided in S.3.2. The applicant should summarize the actual and potential impurities most likely to arise during manufacture, purification, and storage of the drug substance. Impurities of all kinds (e.g., organic, inorganic, residual solvents) should be discussed. For drug substances of biological origin and semisynthetic drug substances, the description of impurities should include, if appropriate, those related to the natural origin of the material (e.g., pesticide residues, heavy metals due to the concentration of metals by certain plant species, related substances whose concentrations vary with changes in harvesting conditions (species, location, season, organ)). The discussion should identify organic impurities as:

- Impurities observed in the drug substance (both identified and unidentified)
- Substances that are considered potential impurities but that have not been observed in the batches of drug substance manufactured
- Impurities that were once present in the drug substance but that have been eliminated by process modifications
- Degradation products observed in stability and stress studies on the drug substance or following processing (e.g., micronization)

The type of information provided for each impurity can vary with the nature of the impurity, the analytical procedure by which it is detected, whether it is actually present in significant quantities in the drug substance, whether it has been identified, and the methods used to identify the impurity.

Evaluation of inorganic impurities and residual solvents should primarily be guided by knowledge of the method of manufacture of the drug substance. Factors that should be considered in evaluating potential sources of organic impurities include the route of synthesis, impurities in the starting materials or biological source materials, possible side reactions, and potential degradation pathways.

Attempts should be made to identify all impurities found in significant quantities in the drug substance. The studies to characterize these impurities should be described. FDA regulates a variety of drug substances; no single recommendation applies to all drug substances for the level of an impurity that would warrant identification. Recommendations on identification levels may be provided for specific situations. For example, *ICH Q3A Impurities in New Drug Substances* recommends thresholds for the identification and qualification of organic impurities for synthetic new drug substances. As discussed in the guidance, however, those thresholds are not necessarily appropriate for potential impurities that are expected to be unusually potent. An applicant is encouraged to discuss any questions about the identification of impurities with the appropriate review divisions.

The following are typical of the information that should be provided for impurities:

- Identity of the impurity or potential impurity (chemical name and structure)
- Analytical procedure used to detect or search for the impurity or potential impurity
- An indication as to whether a potential impurity was actually detected in significant quantities in the drug substance (a detailed accounting of the impurities found in various batches should be provided in S.4.4)
- Structural characterization data and/or other data on the physical or chemical properties of the impurity or potential impurity
- Summary of the route of synthesis or method of preparation if the impurity or potential impurity was independently prepared
- A summary of the attempts made to identify an impurity if it has not been possible to identify it
- A table listing the qualified level of expected impurities with a cross-reference to the appropriate studies (including study numbers and batch numbers). A similar table should be provided in section 3.4 of module 4.

For naturally derived protein drug substances, additional information on product-related and process-related impurities should be provided as recommended in the ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.*

Information concerning the removal or inactivation of adventitious agents in drug substances obtained from animal sources (including semisynthetics that originate from an animal source) should be provided in Appendix A.2 of the application (see section X.B).

Additional guidance is available in:

- ICH: *Q3A Impurities in New Drug Substances*
- ICH: *Q3C Impurities: Residual Solvents and Q3C Tables*
- ICH: *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL10 Impurities in New Veterinary Drug Substances*
- VICH: *GL17 Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products*
- VICH: *GL18 Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances, and Excipients*

VI. CONTROL OF DRUG SUBSTANCE (S.4)

A. Specification (S.4.1)

The proposed specification for the drug substance should be provided. The drug substance specification of the drug substance manufacturer, drug product manufacturer, and/or applicant should be included in this section, as appropriate. The specification included in this section (S.4.1) should be for the drug substance used to produce the drug product. If the drug substance is processed (e.g., micronized) before it is used to manufacture the drug product, the specification for the unfinished drug substance, if there is one, should be included in section in S.2.4. If a physical mixture of two or more drug substances is used to produce the drug product, the specifications for the individual drug substances should be included in S.4.1 of the application. The specification for the mixture should be include in P.3.4 of the application.

The specification establishes criteria to which each batch of drug substance should conform to be considered acceptable for its intended use. *Conformance to specification* means that the drug substance, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. A specification is one part of the strategy to control drug substance quality. The specification is proposed and justified by the drug substance manufacturer and applicant. Drug substance specifications are part of the approved application. Specifications are established to confirm the quality of drug substances rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring the quality of the drug substance as it relates to safety and efficacy of the drug product**.** Information on periodic quality indicator tests is provided below.

The specification sheet should list all tests to which each batch of a drug substance will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. If an analytical procedure will be used only to generate stability data the analytical procedure should be described in S.7.3. Justified interim acceptance criteria and tests with sunset provisions should be included in the specification (see section VI.E). The specification from the applicant and/or drug product manufacturer should identify the tests that it will routinely perform and the test results that will be accepted from the drug substance manufacturer's certificate of analysis (COA).[18] Presentation of information in a tabular format is suggested. The specification sheet should also identify:

[18] The applicant and/or drug product manufacturer must establish the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(2)). The reliability of the analyses need not be established at the time the application is submitted. However, the specification should indicate the tests that will be performed once the reliability of the supplier's results has been established in accordance with current good manufacturing practices.

- Tests that can be performed in-process (e.g., Process tests, intermediate tests, postsynthesis material tests, unfinished drug substance tests) in lieu of testing the drug substance (the results of such tests should be included in the batch analysis report (e.g., Certificate of analysis))
- All analytical procedures that will be used for a test; identifying which are regulatory and which are alternative analytical procedures when multiple analytical procedures can be used for a test[19]
- Acceptance criteria for the test using the regulatory analytical procedure and acceptance criteria for any alternative analytical procedures
- Release and shelf-life acceptance criteria when both are used

An illustrative example of a specification sheet is provided in tables 1 and 2, below.

Table 1: Specification for Synthesized Drug Substance X

Tests	Acceptance Criteria	Regulatory Analytical Procedure	Alternative Analytical Procedure
Appearance	White crystalline powder	Visual	
Identification Tests	Regulatory Analytical Procedure: (1) Retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation obtained as specified in the assay. (2) Spectra is similar to that of corresponding preparation of the reference standard (3) Responds to the tests for sulfate Alternative Analytical Procedure: Conforms to established spectral library	(All performed) (1) HPLC, AP[1] # EFG (2) Infrared Absorption, USP <197M> (3) Sulfate, USP <191>	Near Infrared Analysis[2], AP # ABC
Melting Range	100° to 102°C	AP #BCD	USP <741>, Class Ib
Residue on Ignition	NMT[3] 0.1%	USP <281>, ignition temp. 225°C	
Heavy Metals	0.001%	USP <231>, Method II	
Loss on Drying	NMT 1.0%	USP <731>, dry at 45°C to a constant weight	
Assay	NLT[4] 98.0% and NMT 102.0% of	HPLC, AP # EFG	

[19] Certain *General Chapters* in the USP contain a statement that the text of the USP is harmonized with the corresponding texts of the *European Phamacopoeia* (EP) and the *Japanese Pharmacopoeia* (JP). However, where a difference appears, or in the event of dispute, the result obtained from the USP procedure is conclusive.

Table 1: Specification for Synthesized Drug Substance X			
Tests	Acceptance Criteria	Regulatory Analytical Procedure	Alternative Analytical Procedure
	$C_xH_xN_xO_x$, calculated on the dried basis		
Organic Impurities Specified Impurities • Impurity A • Impurity B • Impurity at RRT[5] XX Unspecified Impurities • Any Unspecified Total Organic Impurities	 NMT 0.3% NMT 0.4% NMT 0.3% NMT 0.1% NMT 1.0%	HPLC; AP # EFG	
Residual Solvent A	NMT 200 ppm in Drug Substance X or NMT 200 ppm in Intermediate C	GC, AP # XYZ	
Particle Size Distribution (D) • D (10%) • D (50%) • D (90%)	 NMT 5 microns NMT 10 microns NMT 30 microns	Brand X Particle Size Analyzer AP # LMN	

[1] AP = Analytical Procedure
[2] Test will be performed on-line during final drying operation.
[3] NMT = not more than
[4] NLT = not less than
[5] RRT = relative retention time

Table 2: Specification for a Highly Purified Naturally Derived Protein Drug Substance Y[1]		
Tests	Acceptance criteria	Regulatory Analytical Procedure (AP)[2]
Appearance	White lyophilized powder	Visual
Identification Tests:		
Identification Test #1	Retention time of the major peak corresponds to that of the reference standard	RP-HPLC[3], AP # A123
Identification Test #2	Retention time of the major peak corresponds to that of the reference standard	SE-HPLC[4], AP # B345
Identification Test #3	Major bands of sample correspond to major bands of the reference standard and account for NLT[5] 85% of total signal	Isoform pattern by isoelectric focusing/Coomassie Blue staining and scanning, AP # C678
Assays:		
Monomer	NLT 95%	SE-HPLC, AP # B345
Specific Biological Activity	20,000-30,000 International Units (IU)/mg	Mouse Bioassay, AP # D901 and Lowry, AP# D902
Purity Tests:		
Dimers and aggregates	NMT[6] 2%	SE-HPLC, AP # B345
Oxidized Forms	Area of the peaks corresponding to oxidized forms is NMT 3% of the sum of peak areas of intact and oxidized products	RP-HPLC, AP # E234
Electrophoretic purity	No additional significant band (NMT 2%) when	SDS-PAGE[7] dissociated and

Table 2: Specification for a Highly Purified Naturally Derived Protein Drug Substance Y[1]

Tests	Acceptance criteria	Regulatory Analytical Procedure (AP)[2]
	compared to the profile of the reference	non-dissociated/silver stain, AP # F567
Bacterial endotoxins	NMT 100 Endotoxin Units (EU)/mg	USP <85>, Gel-Clot Techniques
Microbial Limits	NMT 10 Colony Forming Units (CFU)/10 mg Absence of specified indicator organisms	USP <61>, Plate Method
Water Content	NMT 5% (w/w)	USP <921>, Method Ia
pH	7.0-8.0 in a solution containing 10 mg of Drug Substance Y/mL	USP<791>

[1]This is an example specification and is not intended to imply that these are the typical tests and acceptance criteria for a naturally derived protein drug substance. The tests and acceptance criteria appropriate for a particular naturally derived protein drug substance depend on the biological source, manufacturing process, and its intended use. For example, (1) residual monoclonal antibody (mAbs) should be monitored for drug substances purified by affinity chromatography using mAbs; (2) for proteins that are not as highly purified, less vigorous acceptance criteria for purity tests may be appropriate; and (3) the need for bacterial endotoxins and microbial limits testing and the associated acceptance criteria depend on the route of administration of the drug product and the controls used during the manufacture of the drug product.
[2]There are no alternative analytical procedures specified for Drug Substance Y
[3]RP-HPLC = reverse phase high-pressure liquid chromatography
[4]SE-HPLC = size exclusion high-pressure liquid chromatography
[5] NLT = not less than
[6] NMT = not more than
[7]SDS-PAGE = Sodium dodecyl sulfate polyacrylamide gel electorphoresis

- **Periodic Quality Indicator Tests**

The CGMP regulations require that each batch of drug substance will be tested for conformity with the appropriate written specification; a batch that does not meet the specification must not be used to manufacture the drug product (21 CFR 211.84). Occasionally and when justified, other tests and associated acceptance criteria and analytical procedures that assess drug substance quality can be included in the application and not be listed in the drug substance specification. These tests, referred to as periodic quality indicator tests (PQITs), augment the drug substance specification. A PQIT is performed at release on preselected batches and/or at predetermined intervals, rather than on a batch-to-batch basis. A PQIT can be warranted when a test, performed and reported as part of the batch analysis, has value as an indicator of drug substance quality, but information indicates that the test need not to be performed on each batch of drug substance considering the specific drug products in which the drug substance is used. Designation of certain tests such as for description, identification, assay, or impurities as PQITs would not be considered appropriate. PQITs, along with the drug substance

specification, form a basis for approving the application (see, for example, section 505(b)(1)(D) and 505(d)(3) of the Federal Food, Drug, and Cosmetic Act).[20]

Sufficient data should be available to support a proposal to designate a test as a PQIT. If sufficient data (e.g., data from multiple batches, all proposed manufacturing sites and processes) are available, a PQIT proposal can be included in the original application. A proposal for a PQIT should include:

- The reason the PQIT is being proposed
- Justification and data to support the periodic testing
- The protocol (e.g., Frequency) for performing the test, including when postapproval changes are implemented
- A commitment

The commitment should state that:

- The PQIT will be performed according to the protocol approved in the application.
- Failure to meet the acceptance criteria for the PQIT will be handled (e.g., Investigation, batch rejection decision) in the same manner as a failure of a test included in the drug substance specification and the PQIT will be performed on each subsequent batch until the failure is resolved.
- Any investigation will assess the effect on all batches produced, in particular, the batches between the last batch tested with a passing test result and the batch that failed.
- If the result of the investigation confirms a batch failure or is inconclusive, a changes- being-effected supplement will be submitted to include the test in the drug substance specification.

A list of PQITs, with associated acceptance criteria and reference to analytical procedures, should be included in S.4.1 of the application. The protocol and commitment should also be included in S.4.1. Data and justification to support the designation of a PQIT should be included in S.4.4 and S.4.5, as appropriate. The recommendations on CMC information that should be provided in S.4.2 and S.4.3 also apply to PQITs.

It is recognized that only limited data may be available at the time of submission of an application. Therefore, this concept would generally be implemented postapproval once sufficient data are available and after approval of a prior approval supplement.

[20] 21 U.S.C. 355 (b)(1) and 355 (d)(3).

Additional guidance is available in:

- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

B. Analytical Procedures (S.4.2)

The analytical procedures used for testing a drug substance should be provided. Recommendations on the content and format of analytical procedures submitted in NDAs and ANDAs will be provided in a forthcoming CDER/CBER guidance on *Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation*. Information should be provided for all analytical procedures listed in the specification (S.4.1). The following additional guidance is provided on submitting analytical procedure information from published sources.

- **Analytical Procedures from an Official Compendium or Another FDA-Recognized Standard Reference**

If the analytical procedure used is in the current revision of an official compendium or another FDA-recognized standard reference (e.g., AOAC International Book of Methods) and the referenced analytical procedure is not modified, the analytical procedure need not be provided. A specific citation to the analytical procedure is sufficient.[21] When a general chapter or monograph included in an official compendium or other FDA recognized standard reference allows for the use of more than one analytical procedure for a test, the specific analytical procedure that will be used should be cited here (S.4.2) and in the specification (S.4.1). For example, when using USP <921> *Water Determination,* the method should be specified (e.g., Method Ia). If an analytical procedure is based on one of these sources but has been modified, the analytical procedure should be provided.

- **Analytical Procedures from Other Published Sources**

Analytical procedures from any other published source (e.g., another country's compendium, scientific journal) should be provided.

[21] The current revision of an analytical procedure in a compendial monograph or general chapter should be used. Therefore, when citing an official compendium, the version of the compendium should not be included in the citation. For example, the *USP* should be cited rather than *USP 25*.

Additional guidance is available in:

- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL1 Validation of Analytical Procedures: Definition and Terminology*

C. Validation of Analytical Procedures (S.4.3)

Analytical validation information, including experimental data (e.g., representative chromatograms with peak identification), for the analytical procedures used for testing the drug substance should be provided. Validation of an analytical procedure is the process of demonstrating that analytical procedures are suitable for their intended use. This information should be provided for all analytical procedures listed in the specification (S.4.1). Stability data (S.7.3), including data from stress studies, should be used to support the validation of the analytical procedures. Recommendations on the analytical validation information that should be submitted in NDAs and ANDAs will be provided in a forthcoming CDER/CBER guidance on *Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation*. The methods validation package should be provided in R.3.S.

Additional guidance is available in:

- FDA: *Submitting Samples and Analytical Data for Methods Validation*
- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q2B Validation of Analytical Procedures: Methodology*
- ICH: *Q3A Impurities in New Drug Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL1 Validation of Analytical Procedures: Definition and Terminology*
- VICH: *GL2 Validation of Analytical Procedures: Methodology*

D. Batch Analyses (S.4.4)

A description of relevant batches and results of batch analyses should be provided. Batch analysis reports (e.g., certificates of analysis (COAs)) should be provided for all drug substance batches used for (1) nonclinical studies (i.e., pharmacology and/or toxicology), (2) drug product clinical efficacy and safety, bioavailability, bioequivalence, and (3) primary stability studies. Batch analysis data should also be provided for any other batches that are being used to establish or justify specifications and/or evaluate consistency in manufacturing. The batch analysis reports and collated batch analyses

data should include a description of the batches. This information can be presented (1) with the batch data as space permits or (2) in a separate table with only the batch identity being included with the batch data. The description should include:

- Batch identity (i.e., batch number) and size
- Date of manufacture
- Site of manufacture
- Manufacturing process (e.g., synthetic route A), where applicable
- Use of batch (e.g., bioavailability, stability)

Test results should be expressed numerically or qualitatively (e.g., white crystalline powder), as appropriate. We discourage the use of terms such as *conforms* or *meets specification*.

1. Batch Analysis Reports

The batch analysis reports should include results from all tests performed on the batch, including tests that are not part of the proposed specification. References to analytical procedures should be provided.

A summary of any changes in the analytical procedures should be provided if the analytical procedures (1) changed over the course of generating the batch analyses data and/or (2) are different from the analytical procedure included in S.4.2. The summary should identify when an analytical procedure changed, the differences between the analytical procedures, and the impact of the differences with respect to the data being reported. For example, a summary could state that the solvent system for the assay was changed on December 15, 1999, from A to B so that impurities Y and Z that co-elute using System A could be quantitated separately. If there are significant differences in the analytical procedures (e.g., different fundamental principles such as titration and HPLC), a more detailed summary describing the changes may be warranted.

2. Collated Batch Analyses Data

Presentation of results from all batches for a particular test in tabular and/or graphical format is often helpful in justifying the acceptance criteria. Collated batch analyses data are not warranted for all tests. However, collated data should be provided for assay and impurities (e.g., degradation products, residual solvents) and should be considered for other tests such as water content.

Additional guidance is available in:

- ICH: *Q3A Impurities in New Drug Substances*
- ICH: *Q3C Impurities: Residual Solvents and Q3C Tables*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL10 Impurities in New Veterinary Drug Substances*
- VICH: *GL18 Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances, and Excipients*

E. Justification of Specification (S.4.5)

Justification for the proposed drug substance specifications should be provided. The justification should be based on relevant development data (S.2.6), information on impurities (S.3.2), standards in an official compendium, batch analyses data (S.4.1), stability studies (S.7), toxicology data, and any other relevant data. The discussion in this section should unify data and information that are located in other sections of the application, either by reference or in summary. When justifying the specification, an applicant should consider data from (1) drug substance batches used in evaluating clinical efficacy and safety, bioavailability, and/or bioequivalence, (2) primary stability batches, and (3) relevant development and process validation batches, when available. If multiple drug substance manufacturing sites or processes are planned, it can be valuable to consider data from these sites and processes in establishing the tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug substance at any particular site or by any particular method. Justification for an in-process test that is used in lieu of a drug substance test should be included in S.2.4.

- **Tests**

Inclusion of a test in the drug substance specification need not be justified. However, exclusion of a test that is normally performed on a type of drug substance, one that is recommended in a relevant FDA guidance, or one that was reported in the batch analyses (S.4.4) should be justified. Justification for the designation of a test as a periodic quality indicator test also should be provided (see section VI.A).

Occasionally, it may appear that a test performed and reported as part of the batch analyses may not be necessary or that a drug substance characteristic may not be critical to the quality of the specific drug products in which the drug substance is used. For example, the available test results for heavy metals may be very low or below the limit of

detection of the analytical procedure for the batches produced in support of the application indicating that there may be no need to perform the test. However, it is not certain if the same type of results will continue to be observed for production batches because (1) limited data are available at the time the application is submitted and/or (2) the manufacturing process for production batches will be different (e.g., scale, equipment) from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized. In these or similar circumstances, an applicant could propose a *sunset test protocol* for a test, which would provide for the test to be dropped from the specification after an agreed number of production batches have met certain criteria.[22] The proposal should include the (1) reason why the sunset provision is being proposed; (2) number of consecutive production batches that will be tested before inclusion of the test in the drug substance specification is reevaluated; (3) criteria that would be achieved, including data analysis plan, for the test to be dropped; and (4) postapproval reporting mechanism for notifying FDA of the test results when the criteria have been achieved. A *sunset test protocol* could also be considered when FDA requests that a test be added to the specification.

- **Acceptance Criteria**

Justification should be provided for all proposed acceptance criteria included in the drug substance specification. Results from nonclinical (pharmacology and/or toxicology), clinical, and stability studies and manufacturing and analytical capability should be considered when proposing acceptance criteria. Proposed acceptance criteria can include a reasonable allowance for analytical and manufacturing variability. The justification should discuss the basis of the proposed acceptance criteria from the perspectives of available data and analytical and manufacturing capability and variability. Furthermore, any statistical approaches that are used to establish the acceptance criteria should be described.

Occasionally, an applicant may wish to propose *interim acceptance criteria* for a specific test because there is some uncertainty whether the same type of results will continue to be observed for subsequent drug substance batches. This uncertainty often occurs when (1) there are limited data available at the time the application is submitted and/or (2) the manufacturing process for production batches will be different (e.g., scale, equipment) from that used to produce the batches used to support the application and the effect, if any, of the differences has yet to be characterized. The proposal should include the (1) reason why the interim acceptance criteria are being proposed, (2) number of consecutive batches from each process (if alternative processes are used) that will be tested and/or the time frame before the acceptance criteria will be finalized, (3) data analysis plan, and (4) proposed reporting mechanisms for finalizing the acceptance criteria when the proposed final acceptance criteria are tighter, broader, or the same as the interim acceptance criteria. An applicant should not propose using interim acceptance criteria as a substitute for providing recommended or agreed upon (e.g., at pre-NDA meetings) information in

[22] A proposal to drop a test, based on historical data, can also be submitted postapproval in a prior approval supplement.

an application. For example, proposing interim acceptance criteria would not be appropriate when the stability data package recommended in the ICH guidance *Q1A Stability Testing of New Drug Substances and Products* or VICH guidance *GL3 Stability Testing of New Veterinary Drug Substance and Medicinal Products* has not been provided.[23] For NDAs, finalization of interim acceptance criteria will be a phase 4 commitment.

The proposed acceptance criteria for impurities should not be greater than the levels qualified through nonclinical or clinical studies presented in the NDA. The qualified level of each impurity that is individually listed in the drug substance specification should be provided in S.3.2. Appropriate qualified levels can be obtained from published toxicology studies or guidance documents. Acceptance criteria for residual solvents should generally be based upon manufacturing capability. An applicant should consider the contribution of residual solvents in its drug product excipients when proposing acceptance criteria for residual solvents in the drug substance. See ICH *Q3C Impurities: Residual Solvents* or VICH *GL18 Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances, and Excipients.*

- **Analytical Procedures**

The analytical procedures listed in the drug substance specification normally need not be justified because the appropriateness of the procedure is supported by information in S.4.2, S.4.3, and R.3.S. In some instances, however, justification for the type of analytical procedure used would be warranted. For example, justification should be provided for the use of a nonstability-indicating assay procedure. The justification should explain the scientific reasons why a stability indicating procedure is not viable or warranted (e.g., inorganic salts) and, when appropriate, which analytical procedures complement the assay procedure by qualitatively and/or quantitatively monitoring impurities, including degradants.

Additional guidance is available in:

- ICH: *Q3A Impurities in New Drug Substances*
- ICH: *Q3C Impurities: Residual Solvents and Q3C Tables*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL10 Impurities in New Veterinary Drug Substances*
- VICH: *GL18 Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances, and Excipients*

[23] For those applications that fall within the scope of these guidances.

VII. REFERENCE STANDARDS OR MATERIALS (S.5)

Information on the reference standards or reference materials used for testing of the drug substance (active moiety) should be provided. If the reference standard is obtained from an official source, this should be stated. When the reference standard is not from an official source, it should be fully characterized. Recommendations on the information that should be provided for reference standards will be provided in a forthcoming CDER/CBER guidance for industry on *Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation*. A list of any available reference standards for impurities and intermediates should be included in S.5. [24]

Additional guidance is available in:

- ICH*: Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

VIII. CONTAINER CLOSURE SYSTEM (S.6)

A description of the container closure system for the drug substance should be provided, including the identity of materials of construction of each primary packaging component and its specification. The same type of information should be provided for functional secondary packaging components as is provided for primary packaging components. For nonfunctional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light, [25] compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction. Stability data used to support the suitability of the container closure systems should be provided in S.7.3 and referenced in S.6.

[24] Whether or not information is included in the application, complete records must be maintained of any testing and standardization of laboratory reference standards (21 CFR 211.194(c)).

[25] Data, such as light transmission data, would be provided in S.6. Results from photostability studies, when warranted, should be provided in S.7.3 and cross-referenced in this section (S.6).

Additional guidance is available in:

- FDA: *Container Closure Systems for Packaging Human Drugs and Biologics*

IX. STABILITY (S.7)

Information relating to the stability of the drug substance should be provided in S.7.

A. Stability Summary and Conclusions (S.7.1)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The discussion should include for example (1) a summary of stability batches tested, storage conditions used, attributes tested, shelf-life acceptance criteria, test schedule, amount of data available, and analysis of data (including a summary of the statistical analysis if performed) and (2) conclusions regarding the label storage conditions and retest or expiration dating period, as appropriate.

B. Postapproval Stability Protocol and Stability Commitment (S.7.2)

A postapproval stability protocol and stability commitment should be provided.

C. Stability Data (S.7.3)

Results of stability studies, including statistical analysis if performed, should be presented in an appropriate format (e.g. tabular, graphical, narrative). An applicant should propose a retest or expiration dating period and appropriate label storage conditions for the drug substance. There should be a direct link between the proposed, retest or expiration dating period and proposed label storage conditions and the demonstrated stability characteristics of the drug substance.

1. Primary Stability Studies

The results from long-term, accelerated and, when performed, intermediate studies undertaken on primary batches should be provided. Stability study reports should also be included.

The analytical procedures used to generate the data should be identified. Information on the analytical procedures used to generate the data should be included in this section of the application as follows:

- The analytical procedure, validation of analytical procedures and justification of acceptance criteria, as appropriate, should be included if the analytical procedure listed in the stability protocol is different from the analytical procedure described in S.4 for the corresponding test (i.e., batch release versus stability analytical procedure), or if a test included in the stability protocol is not described in S.4.

- A summary of any changes in the analytical procedures should be provided if the analytical procedure was changed over the course of generating the stability data. The summary should identify when an analytical procedure changed, the differences between the analytical procedures, and the impact of the differences with respect to the data being reported. For example, a summary could state that the solvent system for the assay was changed on December 15, 1999, from A to B so that impurities Y and Z that co-elute using System A could be quantitated separately. If there are significant differences in the analytical procedures (e.g., different fundamental principles such as titration and HPLC) a more detailed summary describing the changes may be warranted.

2. Supporting Stability Studies

Data, other than those from primary stability studies, that support the analytical procedures, the proposed retest date or shelf life, and label storage statements can be provided. Such data can include, for example, stability data on small-scale batches of drug substance or manufacturing processes not proposed for production batches. Stability data to support holding times for intermediates or during processing should also be provided in this section when warranted (e.g. certain proteins). The analytical procedures should be identified, and when analytical procedures are different from those described elsewhere in the application, information should be provided on the analytical procedures to the extent warranted to support the use of the data.

3. Stress Studies

Any results from drug substance stress testing should be provided in this section of the application. The design of the stress studies should be discussed briefly. The information should be used, as appropriate, to support the validation of analytical procedures (S.4.3), the impurities acceptance criteria and/or characterization of expected impurities (S.3.2, S.4.1), justification of the drug product specification (S.4.5), and stability summary and conclusions (S.7.1 and S.7.3).

Additional guidance is available in:

- FDA: *Submitting Documentation for the Stability of Human Drugs and Biologics*[26]
- ICH: *Q1A Stability Testing of New Drug Substances and Products*
- ICH: *Q1B Photostability Testing of New Drug Substances and Products*
- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q2B Validation of Analytical Procedures: Methodology*
- ICH: *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*
- VICH: *GL1 Validation of Analytical Procedures: Definition and Terminology*
- VICH: *GL2 Validation of Analytical Procedures: Methodology*
- VICH: *GL3 Stability Testing of New Veterinary Drug Substance and Medicinal Products*
- VICH: *GL5 Stability Testing: Photostability Testing of New Veterinary Drug Substance and Medicinal Products*
- VICH: *GL17 Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products*

X. APPENDICES (A)

When warranted, information relating to both drug substances and drug products should be included in the Appendices (section A) of the NDA or ANDA or appropriate section of the NADA or ANADA. If drug substance and drug product information is provided in an appendix, the preferred presentation is drug substance information followed by drug product information (e.g., A.1 drug substance then drug product, followed by A.2). The recommendations provided below relate to drug substances. Recommendations on the information to include in the Appendices for drug products will be provided in the forthcoming drug product guidance.

A. Facilities and Equipment (A.1)

Information on facilities and equipment, in addition to the information provided in other sections of the application (e.g., S.2.1, S.2.2), is usually not needed. However, for naturally derived protein drug substances, or when contamination with viral adventitious agents or transmissible spongiform encephalopathy (TSE) agents is a concern, additional information can be warranted and should be included in this section of the application.

- **Viral Adventitious Agents and TSE Agents**

[26] In June 1998 (63 FR 31224), the Agency made available a draft revision of this guidance entitled *Stability Testing of Drug Substances and Drug Products*. When finalized, this revision will be the primary reference source on stability testing of drug substances and drug products.

All developmental or marketed drug substances manufactured or processed in the same areas as the applicant's drug substance should be identified when there is potential for cross-contamination with TSE agents or viral adventitious agents. Information should be included on the design features of the facility and procedures to prevent cross-contamination of areas and equipment.

If bovine-derived materials from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are used or manipulated in the same facility, additional information should be provided, such as whether dedicated equipment is used.

- **For Naturally Derived Protein Drug Substances**

A diagram should be provided illustrating the manufacturing flow, including movement of raw materials, personnel, waste, and intermediates in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the drug substance (e.g., cross contamination).

Information on all development or marketed drug substances manufactured or manipulated in the same areas as the applicant's drug substance should be included.

A summary description of the product-contact equipment and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilization, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment where drug substance manufacturing is performed.

For biotechnology-derived protein drug substances, additional recommendations will be provided in the forthcoming guidance on the submission of CMC information for a therapeutic recombinant DNA-derived product or a monoclonal antibody for in vivo use.

B. Adventitious Agents Safety Evaluation (A.2)

Information assessing the risk with respect to potential contamination with adventitious agents should be provided. The recommendations provided below relate to the drug substance. Recommendations on the information to include in A.2 for drug product will be provided in the forthcoming drug product guidance. For example, if viral safety evaluation studies are performed as part of the drug substance manufacturing (e.g., assessment of a starting material from an animal source), the applicant should refer to the drug substance guidance. However, an applicant should refer to the forthcoming drug product guidance for recommendations when the studies are performed as part of the drug product manufacturing (e.g., assessment of a biotechnology-derived excipient).

For synthetic or semisynthetic drug substances, reduced testing of materials or drug substance and/or validation of removal and/or inactivation of adventitious agents can be appropriate in certain instances, with justification. Such instances can include synthetic steps that inactivate adventitious agents. Early dialog with FDA is encouraged in these circumstances.

Furthermore, for biotechnology-derived protein drug substances, additional recommendations will be provided in the forthcoming guidance on the submission of CMC information for a therapeutic recombinant DNA-derived product or a monoclonal antibody for in vivo use.

1. Nonviral Adventitious Agents

The detailed information regarding the routine manufacturing control of adventitious agents, such as bacteria, mycoplasma, and fungi, typically using well-established (e.g., pharmacopoeial) analytical procedures, should be provided in the appropriate sections within Module 3.2.S. If well-established (e.g., pharmacopoeial) analytical procedures are not used, more detailed information regarding the analytical procedures used should also be included in 3.2.S.

With respect to other nonviral adventitious agents, such as transmissiblespongiform encephalopathy agents and prions, the detailed information should be placed in 3.2.A.2.

Certifications and/or certificates relating to the use of bovine-derived materials and sourcing of materials from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) should be provided, as appropriate.

2. Viral Adventitious Agents

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are considered safe and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable.

Information essential to evaluate the virological safety of materials of animal or human origin (e.g., biological fluid, tissue, organ) should be provided. See related information in section IV.C.

The selection of virological tests that are conducted during manufacturing (e.g., unprocessed bulk, post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture (including drug substance release if possible), that the product is free from viral contamination should be provided. (See related information in section.) Results for viral testing of unprocessed bulk should be included.

The rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses (see related information in section IV.E).

Additional guidance is available in:

- ICH: *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

XI. REGIONAL INFORMATION (R)

When warranted, information relating to both drug substances and drug products should be included in the Regional Information section (section R) of the NDA or ANDA or appropriate section of the NADA or ANADA. The recommendations provided below relate to drug substances. Recommendations on the information to include in the Regional Information section for drug products will be provided in the forthcoming drug product guidance**.**

A. Executed Production Records (R.1.S)

An executed batch record is not required, but if an executed production record is provided for illustrative purposes, it should be included in R.1.S.

B. Comparability Protocols (R.2.S)

A comparability protocol is a protocol describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of postapproval manufacturing changes on the identity, quality, purity, and potency of the drug substance as these factors may relate to the safety and effectiveness of the drug product. Comparability protocols are optional. If a comparability protocol is proposed, it should be included in this section (R.2.S). Approval of a comparability protocol can justify a reduced reporting category for the particular postapproval change described in the protocol.

C. Methods Validation Package (R.3.S)

Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use. Part of the methods validation process can include FDA

laboratory analysis to demonstrate that an analytical procedure is reproducible by laboratory testing. A methods validation package (multiple copies for paper applications) must be submitted in the application (21 CFR 314.50(e)(2) and 314.94(a)(10)) and should be included in this section (R.3.S).

XII. LITERATURE REFERENCES (3.3)

When warranted, references to the scientific literature relating to both drug substances and drug products should be included in the Literature References (3.3) section of the NDA or ANDA or appropriate section of the NADA or ANADA.

The full bibliographic reference should be cited close to where the reference appears in the text of the application (e.g., in a footnote or section endnote). The full text of the literature cited (e.g., journal article) should be included in the Literature References section, except when otherwise indicated. For example, as previously stated in this guidance, monographs from an official compendium need not be included in the application.

ATTACHMENT 1: STARTING MATERIALS FOR SYNTHETIC DRUG SUBSTANCES

A starting material for a synthetic drug substance is a chemical compound of defined molecular structure that contributes to the structure of the drug substance. A reagent that contributes a minor structural element to the drug substance (e.g., hydride ion) is not considered to fall within the meaning of *starting material*. A synthesis can be linear or convergent. Therefore, an applicant should propose one or more starting materials to mark the beginning of each synthesis branch.

The description of the manufacturing process in an application begins with the starting material or materials. Appropriate GMPs, as defined in ICH Q7A, can apply to the manufacturing steps after introduction of the starting material. Because there is limited FDA oversight of the manufacturing of the starting material, the starting material should be selected and controlled so that the risk from future changes in the quality of the starting material affecting the identity, quality, purity, or potency of the drug substance is minimized. A proposed starting material should be chosen so that sufficient information will be available to the FDA on the manufacturing process to evaluate the safety and quality of the drug substance. A drug substance that is used to synthesize another drug substance is not an appropriate candidate for designation as a starting material. An applicant can discuss the selection of proposed starting materials prior to submitting its application. For NDAs, FDA recommends that the choice of starting material be discussed during the investigational period (e.g., at end-of-phase 2 (EOP-2) meeting).

The extent of information that should be submitted in the application to justify the proposed starting materials depends on whether or not the chemical has a significant nonpharmaceutical market. FDA will consider the justification provided to support a proposed starting material as well as other relevant information such as the proposed starting material specification and controls on manufacturing steps downstream from the proposed starting material when evaluating the appropriateness of a proposal to designate a chemical as a starting material.

- **Starting Materials with a Significant Nonpharmaceutical Market**

A significant nonpharmaceutical market is considered to exist if the quantity of the chemical needed for the production of the drug substance represents only a small fraction of the chemical's total market. This is true whether the chemical is made by the drug substance manufacturer for its own use or is obtained from another firm. If the quality of the chemical made for the nonpharmaceutical market is insufficient to ensure consistent quality of the drug substance and the chemical is further processed to produce material of higher quality, the purification operations should be described as part of the manufacturing process of the drug substance (S.2.2). See section II of this attachment for recommendations on the documentation that should be provided for these starting materials.

- **Starting Materials without a Significant Nonpharmaceutical Market**

A chemical should not be considered to have a significant nonpharmaceutical market if (1) the only market for the chemical is to manufacture drug substance; (2) the drug substance manufacturer had to synthesize the chemical, or arrange for another firm to synthesize it, to produce drug substance for clinical trials (phase 1 and phase 2 clinical trials for human drug products); (3) an existing manufacturer of the chemical had to scale up its process to produce sufficient quantities of drug substance for clinical trials (phase 1 and phase 2 clinical trials for human drug products); or (4) the method of manufacture was provided by the drug substance manufacturer to the other firms that manufacture the chemical. See sections I and II of this attachment, respectively, for selection principles and recommendations on the documentation that should be provided for these starting materials.

I. SELECTION PRINCIPLES FOR STARTING MATERIALS WITHOUT A SIGNIFICANT NONPHARMACEUTICAL MARKET

Each proposed starting material without a significant nonpharmaceutical market should be evaluated with respect to the selection principles described in sections I.A through I.D. These principles are intended to assist an applicant in proposing starting materials at a point in the process that ensures the following:

- Sufficient information is submitted in the application for FDA to evaluate the safety and quality of the drug substance.
- Future changes in the manufacture of the starting material are unlikely to affect the safety or quality of the drug substance.

The selection principles should be discussed when justifying proposed starting materials (see II.D.2 of this attachment). If a proposed starting material is inconsistent with a selection principle, this should be justified or the applicant should consider proposing as a starting material a chemical earlier in the manufacturing process that is consistent with the selection principles.

A. Propinquity

A chemical proposed as a starting material should be separated from the final intermediate by several reaction steps that result in isolated and purified intermediates. Having several reaction steps and associated purification and isolation steps separating the starting material and the final intermediate reduces the risk that changes in the manufacturing steps prior to the starting material would adversely affect the identity, quality, purity, or potency of the drug substance as these factors relate to the safety and efficacy of the drug product. For example, the risk of a new starting material impurity (e.g., from a new source or different manufacturing process) being carried over to the drug substance decreases as the number of manufacturing steps between the starting material and the final intermediate increase.

A reaction followed by multiple purifications should be counted as a single reaction step. The reaction step that produces the final intermediate can be counted as a reaction step for purposes of evaluating propinquity if the final intermediate is isolated and purified. An interconversion of a salt to or from its free acid or base form should not be counted as a reaction step for the purpose of evaluating propinquity.

Isolated and purified intermediates are typically obtained by filtration or centrifugation, fractional distillation from a mixture, or chromatographic procedures. A key element in each of these examples is that some removal of organic impurities usually results from the isolation operation. An operation should not be considered to produce an isolated and purified intermediate if some purification of this nature does not simultaneously take place. For example, evaporating solvent from a reaction mixture or the extraction work up of a reaction mixture is not considered to produce an isolated and purified intermediate.

B. Isolated and Purified

A chemical proposed as a starting material should be an isolated and purified substance. Identification of an isolated and purified substance as the starting material, as opposed to an in situ and/or crude substance reduces the risk of degradants and/or impurities affecting the identity, quality, purity, or potency of the drug substance.

C. Carryover of Impurities

A chemical proposed as a starting material should not be the source of significant levels of impurities in the drug substance. Robust acceptance criteria for starting material impurities reduces the risk of a new starting material impurity (e.g., from a new source or different manufacturing process) and/or its associated reaction by-products being carried over to the drug substance in levels that warrant identification and qualification from a safety perspective.

For purposes of selecting proposed starting materials, a significant level is considered to be greater than 0.10 percent in the drug substance (0.20 percent for veterinary drug substances not used in human drug products) of any of the following impurities:

- The proposed starting material
- Impurities in the proposed starting material
- Synthetic derivatives of impurities in the proposed starting material

Moreover, a proposed starting material should be at or before the point in the manufacturing process where transmissible spongiform encephalopathy (TSE) agents can be introduced into the process. For example, if a chemical is produced using an enzyme that can introduce TSE agents into the process, the proposed starting material should be prior to the enzymatic step regardless of whether the chemical is consistent with all other selection principles.

D. Complexity of Structure

A chemical proposed as a starting material should be readily distinguishable from potential isomers and analogs so that adequate controls can be established for the starting materials. There is increased risk to the identity, quality, purity, or potency of the drug substance if a chemical cannot be readily distinguished from its potential isomers and analogs. Moreover, a chemical with a complex molecular structure (e.g., multiple chiral centers) are usually produced through complex synthetic pathways, which can also increase the risk. A proposed starting material typically should possess only a limited number of functional groups and structural features that can result in geometric or stereoisomerism for it to be considered readily distinguishable. It is impossible to set meaningful limits on the maximum number of such elements that a starting material can possess to be considered readily distinguishable. However, data demonstrating that instrumental techniques commonly used for identification tests (e.g., ultraviolet-visible spectrophotometry, infrared spectroscopy) are specific can be provided to justify proposed starting materials that the Agency might otherwise consider to be too complex. If advanced techniques suitable for complex structures (^{1}H-NMR, ^{13}C-NMR, 2D NMR, mass spectrometry, elemental analysis, X-ray crystallography, chiral HPLC) are needed to distinguish the proposed starting material from potential isomers and analogs, the chemical is not an appropriate candidate for designation as a starting material.

II. DOCUMENTATION

Applicants should provide the following information in S.2.3:

A. List of Proposed Starting Materials

The chemical name, CAS Registry Number, structure, molecular formula, molecular weight, and relevant physical characteristics (e.g., appearance, physical state, melting or boiling range) should be provided for each proposed starting material.

B. Flow Diagram of the Complete Synthesis

A flow diagram should be provided showing the complete route of synthesis of the drug substance. Each synthesis branch should begin with chemicals that have a significant nonpharmaceutical market, regardless of whether these chemicals are being proposed as starting materials. The proposed starting materials should be highlighted in the flow diagram.

If all of the proposed starting materials have significant nonpharmaceutical markets, this flow diagram should be the same as the flow diagram provided in S.2.2. The flow diagram in S.2.2 can be cross-referenced**.**

C. Specifications

A specification for each proposed starting material should be provided. Each specification should be based on the quality of the material used to prepare the batches of drug substance used to establish the specification for the drug substance (see sections VI.A, VI.D, and VI.E of this guidance).

Identification tests for a proposed starting material should be specific and should be able to discriminate between it and any related compounds that are likely to be present. More than one identification test may be appropriate. Tests to confirm the presence of a counter ion (e.g., sodium, chloride) should be included in addition to other identity tests.

The specification for a proposed starting material generally should include individual limits on impurities and a limit on total impurities. A limit on unspecified impurities should also be considered. Acceptance criteria for residual solvents and inorganic impurities should also be considered, taking into account the potential for carryover. Moreover, FDA recommends that acceptance criteria be established for all organic impurities that occur above 0.10 percent and that a limit of NMT 0.10 percent be established for unspecified organic impurities when there is greater potential for impurities originating from the starting material to carryover to the drug substance (0.20 percent for a veterinary drug substance not used in human drug products). There can be a greater potential for carryover (1) when the proposed starting material is the first isolated and purified chemical (counting backwards from the drug substance) consistent with the selection principle concerned with the carryover of impurities or (2) based on the proximity of the starting materials to the drug substance.

D. Justification

1. Starting Materials with a Significant Nonpharmaceutical Market

When a significant nonpharmaceutical market exists for a proposed starting material, the discussion of the relationship between the proposed starting materials and the selection principles described in section I of this attachment need not be provided. However, an applicant should be prepared to provide documentation demonstrating that a significant nonpharmaceutical market exists for a proposed starting material. Documentation is more likely to be requested for proposed starting materials with complex molecular structures within a few steps of the drug substance and/or where the extent of use in nonpharmaceutical markets is less obvious. When warranted, this documentation should typically consist of the following:

- A description of the uses other than for drug substance production
- Examples of manufacturers who are able to provide quantities suitable for both drug substance production and other markets
- Confirmation that (1) the drug substance manufacturer did not synthesize the chemical, or arrange for another firm to synthesize it, to produce drug substance

for clinical trials (phase 1 and phase 2 clinical trials for human drug products); (2) an existing manufacturer of the chemical did not scale up its process to produce sufficient quantities of drug substance for clinical trials (phase 1 and phase 2 clinical trials for human drug products); and (3) the method of manufacture was not provided by the drug substance manufacturer to the other firms that manufacture the chemical (i.e., no technology transfer occurred).

2. Starting Materials without a Significant Nonpharmaceutical Market

The justification for starting materials without a significant nonpharmaceutical market should discuss the relationship between each proposed starting material and the selection principles.

Data (e.g., carryover of impurities) used to justify the proposed starting material should be from batches manufactured by the proposed manufacturing process. If data from batches produced by other manufacturing processes are also used, the data should be clearly identified as supporting data and the differences in these manufacturing processes and the proposed manufacturing process should be described.

a. Propinquity

The flow diagram provided in S.2.3 will indicate the separation between the final intermediate and the proposed starting material. A cross-reference to the flow diagram in S.2.3 is sufficient.

b. Isolated and Purified Substances

The starting material specification and the flow diagrams provided in S.2.3 should indicate whether a proposed starting material is an isolated and purified substance. Therefore, cross-reference to this information is sufficient.

c. Carryover of Impurities

Impurities reported in S.3.2 that are found in the drug substance at levels greater than 0.10 percent (0.20 percent for a veterinary drug substance not used in human drug products) should be listed in S.2.3, or a cross-reference should be provided to the information in S.3.2. For each of the listed impurities, information should be provided to demonstrate that the impurity did not originate from the proposed starting material. Such information should consist of, for example:

- Analytical data demonstrating that the impurity is not present in the proposed starting material
- Data indicating that the impurity originates as part of the synthetic process after the introduction of the proposed starting material

- Analytical data to show that the bulk of the impurity found in the drug substance originates from sources other than the proposed starting material, when the assignment of the source of an impurity in the drug substance is uncertain (e.g., An impurity might logically result from the degradation of the proposed starting material, the drug substance, or any of the intermediates in between)

If changes were made in the manufacturing process that follows the introduction of the starting material (e.g., by the addition of a purification procedure or by the repetition of an existing procedure on a routine basis) so that the proposed starting material is not a significant source of impurities in the drug substance, this should be clearly stated in the discussion.

If a firm is not able to identify one or more of the impurities present above 0.10 percent in the synthetic drug substance (0.20 percent for a veterinary drug substance not used in human drug products), an empirical approach can be attempted provided that the proposed starting material can be demonstratively purified by recrystallization or some other technique. Two samples of the proposed starting material, one the quality of the material used to prepare the batches of drug substance used to establish the specification for the drug substance (see sections VI.A, VI.D, and VI.E of this guidance) and one highly purified, can be converted under identical conditions at bench scale to drug substance. If the unidentified impurities are present in both samples of drug substance, this would indicate that they do not originate from impurities in the proposed starting material. If this approach is used, applicants should provide a report documenting all salient aspects of the experiment.

d. Complexity of Structure

Information on the complexity of the structure of the starting material need not be provided for proposed starting materials that possess only a limited number of functional groups and structural features that can result in geometric or stereoisomerism. However, if the chemical structure of the proposed starting material is sufficiently complex, information should be provided to support that the starting material is readily distinguishable from potential isomers and analogs using common instrumental techniques (e.g., ultraviolet-visible spectrophotometry, infrared spectroscopy). Applicants should provide data (e.g., analytical, spectra) comparing the proposed starting material to a reasonable selection of isomers and analogs to demonstrate that the identification tests for the proposed starting material are sufficiently specific.

III. POST APPROVAL ISSUES

When a starting material has been designated in and approved as part of an application, postapproval changes to the manufacturing process of the approved starting materials, including changes in the route of its synthesis, need not be reported to the Agency unless a commitment to report such changes was included in the approved application. Changes in the specification of an approved starting material and changes to the manufacturing process of the drug substance following the introduction of the starting material should be reported to the Agency in accordance with applicable regulations and guidances.

It is valuable for drug substance manufacturers to maintain close communication with manufacturers of starting materials. The quality of a starting material can be affected by changes in manufacturing process (e.g., changes in solvents, purification, catalysts, route of synthesis), and knowledge that a change has taken place can assist a drug substance manufacturer in maintaining a valid starting material specification.

ATTACHMENT 2: STARTING MATERIALS OF PLANT OR ANIMAL ORIGIN

The FDA considers (1) cells; (2) plants, plant parts, macroscopic fungi, or algae; or (3) animal tissues, organs, or body fluid from which the drug substance is derived to be starting material for a drug substance derived from a biological source. Identification of the biological source is warranted to ensure the identity, quality, and purity of the drug substance and to address critical safety issues (e.g., viruses, residual pesticides). The term *drug substance derived from a biological source* includes drug substances that are the chemical obtained directly from the biological source and semisynthetic drug substances that are produced by modification of a chemical (i.e., intermediate) obtained from the biological source. A semisynthetic drug substance can have more than one starting material, depending on the number of branches in the synthetic portion of the manufacturing process. A drug substance is considered semisynthetic when at least one of the starting materials is of biological origin.

The recommendations in Attachment 2 do not pertain to:

- Starting materials that are highly purified chemicals obtained from biological sources that had significant nonpharmaceutical markets before they were used in the drug substance synthesis (e.g., Sucrose, tartaric acid).
- Starting materials of synthetic origin for semisynthetic drug substances
- Cells used in fermentation processes
- Cells or tissue used in cell culture processes
- Transgenic plants or animals

The recommendations in Attachment 1 apply to starting materials of biological origin that have significant nonpharmaceutical markets and starting materials of synthetic origin for semisynthetic drug substances. Starting materials for antibiotics and other cellular metabolites produced by microorganisms using conventional fermentation processes will be covered by a forthcoming guidance.

I. DOCUMENTATION

Applicants should provide the following information in S.2.3 for plant or animal starting materials. For semisynthetic drug substances the information recommended in Attachment 1 should be provided for the starting materials of synthetic origin, if there are any, in addition to the information provided for the plant or animal starting materials.

A. Information on Plant or Animal Starting Materials

The following should be provided for plant starting materials:

- Biological identification (i.e., Family, genus, species, variety) and the process for confirming taxonomic authenticity

- Part of the plant used (e.g., Seed, flower, roots, all)
- Geographic areas of harvesting (e.g., Countries, provinces, states)
- Growing season and harvest time
- List of pesticides and herbicides that may be used in the geographic areas of harvesting
- Supplier (i.e., Company with overall responsibility for collecting biomass, not individual harvesters, plantation owners, or subcontractors)

The following should be provided for animal starting materials:

- Biological identification (i.e., Species)
- Specific part of animal used (e.g., Pancreas, bone, urine)
- Country of origin[27]
- A list of known diseases or pathogens associated with the type of animal
- Criteria for ensuring animal health
- For animals that are consumed for food, a statement of compliance with USDA or equivalent requirements
- Supplier (i.e., Company with overall responsibility for collecting biomass, not individual farmers or subcontractors)

B. Flow Diagram of the Manufacturing Process

When the drug substance is the chemical obtained directly from the biological source this flow diagram should be the same as the flow diagram in S.2.2. The flow diagram in S.2.2 can be cross-referenced.

For semisynthetic drug substances, the flow diagram should depict the manufacturing process that results in the chemical (i.e., intermediate) from the biological source and the synthetic part of the manufacturing process. See Attachment 1, Section II. B for recommendations on the flow diagram for the synthetic part of the manufacturing process.

C. Specifications for Plant or Animal Starting Materials

The specification for the starting material should be based on the quality of the material used to prepare the batches of drug substance used to establish the specification for the drug substance (see sections V.A, V.D, and V.E of this guidance). The specification for plant starting materials should include identity tests for determining taxonomic authenticity and, when appropriate, screening for pesticides and herbicides. The specification for the animal starting material should include screening for adventitious agents, when appropriate.

[27] Bovine-derived materials should not be from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) unless otherwise exempted by the Agency.

A chemical substance (e.g., plant extract) used to produce a semisynthetic drug substance or a crude drug substance derived from a plant or animal starting material is considered an intermediate. Information on the intermediate, including the specification, should be provided in S.2.4.

II. ENVIRONMENTAL ASSESSMENT

All NDAs, ANDAs, NADAs, and ANADAs must include either an environmental assessment (EA) or claim of categorical exclusion from the requirement to provide an environmental assessment (21 CFR 25.15(a)). Environmental information should be included in Module 1 of an NDA or ANDA submitted in the CTD format or the Environmental Impact section of an NADA or ANADA. CDER's position on when an EA should be submitted in the NDA or ANDA to support the use of a drug substance derived from a plant or animal is described in the guidance *Environmental Assessment of Human Drug and Biologics Applications.* Applicants should refer to this guidance, the VICH guidance *GL6 Environmental Impact Assessments (EIAs) for Veterinary Medicinal Products (VMPs)*, and 21 CFR part 25 for additional information on environmental assessments.

III. POSTAPPROVAL ISSUES

Changes in the information on plant or animal starting materials (see section I.A of this attachment) should be reported to the Agency in a prior approval supplement. The supplement should include a new or revised environmental assessment or claim of categorical exclusion from the requirement to provide an environmental assessment, as appropriate. Information should also be provided concerning the potential for the change to result in new impurities or higher levels of known impurities. A change that is merely editorial or administrative (e.g., a change in ownership of the supplier with no change in the process for overseeing collection of biomass) can be submitted in an annual report.

GLOSSARY

Adventitious Agents: For the purpose of this guidance, pathogenic viruses and non-viral agents (e.g., transmissible spongiform encephalopathy agents, pathogenic bacteria, mycoplasma) in plants, animals, or cells or any materials derived therefrom, used in the manufacture of human drug substances or products

Alternative Processes: Two or more manufacturing processes described in an application that can be used to prepare the same intermediate or drug substance

Auxiliary Materials: Substances (e.g., charcoal, filter aid) used during the manufacturing process of a drug substance that are not normally considered to be starting materials, intermediates, reagents, solvents, catalysts, or diluents

Critical: Describes a process step or process control (e.g., process condition, test requirement, or other relevant parameter or item) that must be controlled within predetermined criteria to ensure that the drug substance meets its specification

Crystal Shape (Habit): Crystals with the same internal structure but different external shape because different crystal faces have developed during growth

Degradation Product: A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of, for example, light, temperature, pH, water, and/or by reaction with an excipient (or diluent), another drug substance, and/or the immediate container closure system. Also called decomposition product.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)). The term *drug substance* can also be used to refer to a physical mixture of two or more drug substances used to produce a fixed-combination drug product.

Final Intermediate: In reference to synthetic and semisynthetic drug substances, the last compound synthesized before the chemical reaction that produces the molecule or ion responsible for the physiological or pharmacological action of the drug substance. The chemical reaction that transforms the final intermediate into a form of the drug substance involves more than a change in salt form (including a salt with hydrogen or coordination bonds) or other noncovalent derivatives (such as complex chelates or clathrates).

Identification Threshold: A limit above (>) which an impurity should be identified (ICH Q3A or VICH GL10)

In-process Material Tests: Measures used to assess the quality attributes of an intermediate, postsynthesis material, or unfinished drug substance and/or their suitability for use in the manufacturing process

In Situ Intermediate: An intermediate that is not isolated. It is normally, but not necessarily, in solution

Intermediate:

- For synthetic drug substances, a material produced during steps of the synthesis of a drug substance that undergoes further molecular change before it becomes a drug substance. Intermediates may or may not be isolated (ICH Q3A and Q7A or VICH GL10)

- For drug substances derived from a biological source, a material produced during the manufacturing process of a drug substance that undergoes further purification or molecular modification before it becomes a drug substance

Intermediate Tests: Measures used to assess the quality attributes of an intermediate and/or its suitability for use in the manufacturing process

Operating Parameters: Conditions that can be adjusted to control the manufacturing process (e.g., temperature, pressure, pH, time, mixing speed)

Particle Size Distribution: A measurement of the relative proportion of particles in a sample as a function of size

Physical Properties: Attributes such as physical state, melting point, boiling point, solubility, hygroscopicity, color, density, refractive index, partition coefficient, crystal shape, solid state form, and particle size distribution

Polymorphic Forms: Different crystalline forms of the same drug substance. These can include solvation or hydration products (also known as pseudo-polymorphs) and amorphous forms (ICH Q6A, Q3A)

Postsynthesis Material: For synthetic or semisynthetic drug substances, a postsynthesis material is a material that appears in the process after the final intermediate and before the drug substance (unfinished drug substance or form of drug substance used to produce the drug product). Postsynthesis materials can differ from the drug substance, for example, in stereochemical identity, solid state form, or either the absence of a counterion or the presence of a counterion different from that in the drug substance. Although firms have sometimes referred to such materials as *intermediates*, these materials do not meet the definition of intermediate and final intermediate provided in this guidance for synthetic or semisynthetic drug substances.

Postsynthesis Material Tests: Measures used to assess the quality attributes of a postsynthesis material and/or its suitability for use in the manufacturing process

Process Controls: An all-inclusive term used to describe the controls used during production to monitor and, if appropriate, adjust the process and/or to ensure an intermediate with an established specification or the drug substance will conform to its respective specification. The term includes operating parameters, environmental controls, process tests, intermediate tests, postsynthesis materials tests, and unfinished drug substance tests.

Process Tests: Measures used to monitor and assess the performance of the process (e.g., a test to evaluate reaction progress)

Reaction Step: A unit operation or number of unit operations that effect a change in the molecular structure of a starting material or intermediate. More than one reaction step can take place sequentially in a single reaction vessel.

Residual Solvents: Organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products, that are not completely removed by practical manufacturing techniques (ICH Q3C or VICH GL18)

Retest Period: The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics (ICH Q1A or VICH GL3).

Semisynthetic Drug Substance: A drug substance where structural elements have been introduced by a combination of chemical synthesis and elements of biological origin

Solid State Form: A particular crystalline or noncrystalline structure of a solvated or nonsolvated drug substance. This can include polymorphs, pseudopolymorphs (hydrates or solvates), and amorphous forms.

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents and other components including container closure system and in-process materials. A specification sheet includes the list of tests, reference to analytical procedures, and acceptance criteria.

Starting Material: Materials that mark the beginning of the manufacturing process as described in an application. A starting material for a synthetic drug substance is a chemical compound of defined molecular structure that contributes to the structure of the drug substance. The starting material for a drug substance obtained from a biological source is considered to consist of the (1) cells; (2) plants, plant parts, macroscopic fungi, or algae; or (3) animal tissues, organs, or body fluid from which the drug substance is derived.

Synthesis Branch: A portion of a convergent synthesis that ends with an intermediate that is to be covalently joined with another intermediate or starting material in the next step of the synthesis

Unfinished Drug Substance: A form of the drug substance that is further processed to produce the form of the drug substance used to manufacture the drug product

Unfinished Drug Substance Tests: Measures used to assess the quality attributes of an unfinished drug substance and/or its suitability for use in the manufacturing process

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria (ICH Q7A)