Guidance for Industry

Drug Substance

Chemistry, Manufacturing, and Controls Information

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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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.

366
367

> 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*

368
369
370 **IV. MANUFACTURE (S.2)**
371
372 Information concerning the manufacture of the drug substance, as described below, should be
373 provided in S.2.
374
375 **A. Manufacturers (S.2.1)**
376
377 The name, address, and manufacturing responsibility should be provided for each firm
378 (including contract manufacturers and testing laboratories) and each site (i.e., facility)
379 that will be involved in the manufacturing or testing of the drug substance. Each site
380 should be identified by the street address, city, state, and, when available, the drug
381 establishment registration number.[12] The addresses should be for the location where the
382 relevant manufacturing or testing operation will be performed. Addresses for corporate
383 headquarters or offices need not be provided. Building numbers or other specific
384 identifying information should be provided for multifacility campuses. For sites
385 processing sterile drug substances, the sterile processing area (e.g., room) should also be
386 included. Addresses for foreign sites should be provided in comparable detail, and the
387 name, address, and phone number of the U.S. agent for each foreign drug establishment,
388 as required under 21 CFR 207.40(c), should be included.
389
390 To facilitate preapproval inspection related activities, it is recommended that the name,
391 telephone number, fax number and e-mail address of a contact person be provided for
392 each site listed in the application. Facilities should be ready for inspection when the
393 application is submitted to FDA.
394
395 **B. Description of Manufacturing Process and Process Controls (S.2.2)**
396
397 The description of the drug substance manufacturing process represents the applicant's
398 commitment for the manufacture of the drug substance. A flow diagram and a complete
399 description of the processes and process controls that will be used to manufacture the
400 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

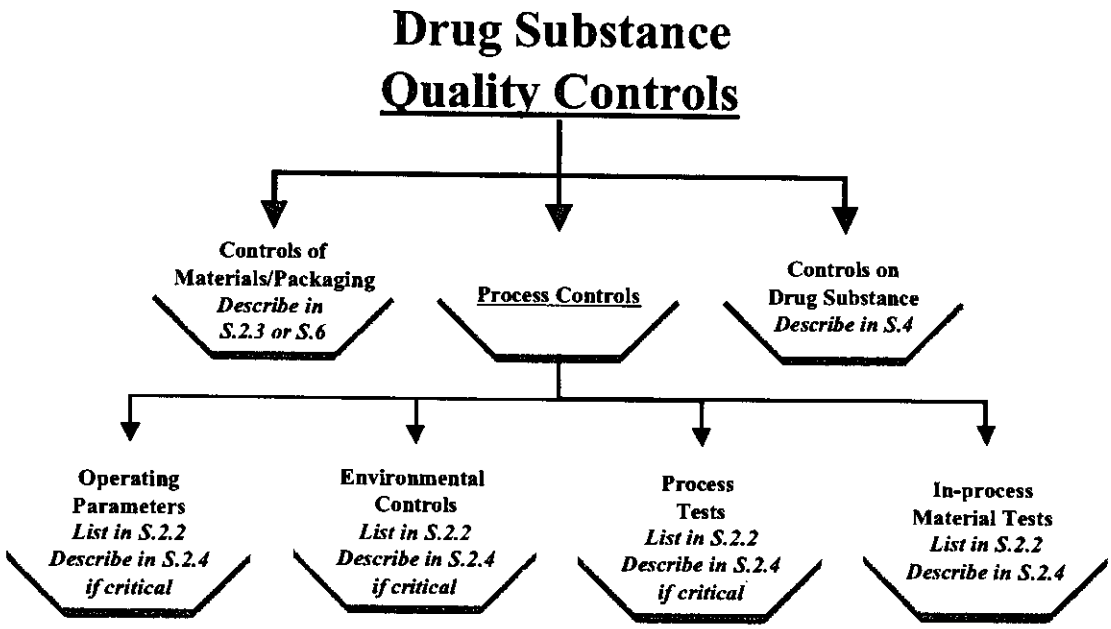
Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. Process tests and in-process material tests can be performed on-line, at-line, or off-line. All process controls, critical or otherwise, should be included in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

665

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*

666
667 **C. Control of Materials (S.2.3)**
668
669 Information on the materials (starting materials, reagents, solvents, auxiliary materials,
670 and diluents) that will be used to manufacture the drug substance or derive it from a
671 biological source, including purification, should be provided in S.2.3. Information
672 indicating where each material is used in the manufacturing process should be provided
673 in the flow diagram and in the narrative description of the manufacturing process (S.2.2).
674
675 When appropriate, specific tests and acceptance criteria to control microbial
676 contamination should be included in the specification for materials used to manufacture
677 drug substances. For materials of biological origin, information assessing the risk with
678 respect to potential contamination with adventitious agents should be provided in
679 Appendix A.2 of the application when appropriate (see section X.B).
680
681 *1. Starting Materials*
682
683 For application purposes, *starting materials* mark the beginning of the manufacturing
684 process described in an application. The starting material for application purposes can
685 differ from the *active pharmaceutical ingredient (API) starting material,* which marks the
686 point in the manufacturing process from which appropriate GMP should be applied (as
687 defined in ICH Q7A: *Good Manufacturing Practice Guidance for Active*
688 *Pharmaceutical Ingredients*). In general, the starting material and API starting material
689 should be the same for a synthetic drug substance. However for a drug substance derived
690 from a biological source, the starting material (e.g., plant) and API starting material (e.g.,
691 extract) can be different. In this case, information on the biological source (e.g., potential
692 pathogens, herbicides, pesticides) is warranted in the application so FDA can evaluate the
693 suitability of the biological source as a starting material for drug manufacture (see
694 Attachment 2). The recommendations for starting materials provided in this guidance are
695 for application purposes. See ICH Q7A for recommendations on API starting materials.
696
697 Starting materials for a synthetic drug substance are chemical compounds of defined
698 molecular structure that contribute to the structure of the drug substance. A proposed
699 starting material for a synthetic drug substance should be chosen so that sufficient
700 information will be available to FDA on the manufacturing process to evaluate the safety
701 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.

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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*

867
868 **E. Process Validation and/or Evaluation (S.2.5)**
869
870 Validation information relating to the adequacy and efficacy of any sterilization process
871 (e.g., drug substance, packaging components) should be submitted in this section of the
872 application for sterile drug substances. Furthermore, if a step in the manufacturing
873 process is designed to reduce the amount of microbial contamination, such as for certain
874 drug substances derived from biological sources, information to support the
875 appropriateness of the step should be included. Submission of other manufacturing
876 process validation information in the application is not necessary for most drug
877 substances.[15] However, for naturally derived protein drug substances, information
878 concerning the evaluation of purification processes related to the removal of impurities
879 should be provided in this section. When applicable, validation information should be
880 provided for processes used to control adventitious agents. This information should be
881 included in A.2.
882
883 Submission of validation information for reprocessing and reworking operations usually
884 is not warranted. However, it can be warranted when the reprocessing or reworking
885 operation is of the type for which process validation information is submitted when
886 routinely performed or when the reprocessing or reworking operations have a significant
887 potential to affect the identity, strength, quality, purity, or potency of the product (e.g.,
888 naturally derived protein drug substances).
889
890 **F. Manufacturing Process Development (S.2.6)**
891
892 A description of the manufacturing process for the drug substance throughout the various
893 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.

Guidance for Industry

Drug Product

Chemistry, Manufacturing, and Controls Information

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 150 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Upinder Atwal 301-827-5848 or (CBER) Christopher Joneckis 301-435-5681.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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January 2003
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Guidance for Industry

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