



## USP Pharmaceutical Ingredient Verification Program

VERIFYING INGREDIENT QUALITY  
for the Pharmaceutical Industry

# ▶ Manual for Participants

## **NOTICE**

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This manual provides information to drug substance manufacturers who wish to participate in the United States Pharmacopeia's Drug Substance Verification Program (USP Drug Substance VP or "Program").

The Program is designed to assist participants in assuring their customers – drug product manufacturers – that the manufactured ingredient is produced in accordance with Good Manufacturing Practices (as defined in this manual) and the participant's other quality controls and systems comply with the ingredient label, and meet other Program requirements. USP considers this to be a cooperative effort between USP and participants. USP welcomes suggestions for improvements to the Program. Participants who meet the requirements of this Program will receive permission to use a special USP Certification Mark in conjunction with a certificate of analysis or similar document. Barring safety concerns or other special circumstances (see section 18 APPEALS), USP maintains the confidentiality of information gained through the verification process in accordance with the provisions of the Program License Agreement.

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## 1. OVERVIEW

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### **The USP's Drug Substance Verification Program (USP Drug Substance VP or "Program")**

is one of several public health programs of the United States Pharmacopeia (USP).

Participation is voluntary and open to participants manufacturing drug substances for use in pharmaceutical products.

The Program covers drug substances used in the manufacture of pharmaceutical products.

The Program includes:

- Evaluation of participants' quality systems through audit of each manufacturing site for compliance with Good Manufacturing Practices (e.g., ICH Q7 *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*)
- Review of manufacturing and quality control documents for each drug substance submitted for verification, including review of characterization, stability, and release data for compliance with labeling and certificate of analysis claims as well as compliance with *USP-NF* monographs as applicable.
- Laboratory testing of drug substance samples from selected lots for compliance with labeling or certificate of analysis claims and program requirements.
- Grant of the Certification Mark upon full satisfaction of Program requirements.
- Post-verification surveillance testing of drug substances bearing the Certification Mark.
- Post-verification audits.
- Periodic re-verification.
- Reporting by participants of changes to the manufacturing or testing of drug substances bearing the Certification Mark.

The use of the distinctive Certification Mark is granted for drug substances that successfully meet Program requirements. The mark indicates the verification of drug substance quality and the adequacy of the participant's quality systems and controls by a trusted and established authority. It provides assurance that:

- The participant has established and is following a quality system that helps to ensure that the drug substance evaluated meets its labeling or certificate of analysis claim for identification, strength, purity, and quality, and is consistent in quality from batch to batch.
- The participant follows accepted manufacturing practices in producing the subject drug substance.
- The tested drug substance samples meet requirements for acceptable limits of contamination and impurities.

## 2. CRITERIA FOR PARTICIPATION

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### Participants in the USP Drug Substance VP must do the following:

- Complete and comply with all provisions of the Program License Agreement.
- Submit requested data and documentation.
- Subject their drug substances and facilities to all reviews, audits, tests, and other requirements specified in the Program.
- Abide by the decisions made by USP and its designees in accordance with the rules and requirements of the Program.
- Operate in accordance with the provisions of all applicable laws and regulations.
- Ensure that drug substances submitted for review meet the requirements specified in *USP-NF* where applicable. In the absence of *USP-NF* standards for such drug substances, ensure that adequate data are submitted for substantiation of the quality of the drug substance(s) and there are analytical procedures in place to perform the necessary tests.
- Provide recall history of submitted drug substances, dating back five years.
- Provide stability data to support the claimed expiration date/retest date of the drug substance.
- Pay all fees required by USP agreements or by documents executed between the participant and USP.
- Act in compliance with the USP Drug Substance Certification Mark Usage Manual that provides (a) rules regarding the placement of the mark on drug substance labeling and certificates of analysis and (b) guidelines for advertising.

### 3. REQUIRED PROCESS AND SUBMISSIONS

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*Please note that all submissions to the Program must be in English. Translations of documents not originally created in English must be certified by the participant.*

**Companies that wish to participate in the Program shall:**

- Appoint a duly authorized representative to execute a "License Agreement."
- Provide the following financial and legal information:
  - Description of any litigation related to the drug substance(s) for which verification is sought, and a description of any pending or threatened litigation against the participant
  - Description of general liability and product liability insurance, including limits expressed in U.S. dollars
  - Results of audits performed by government regulatory agencies during the past three years, including the United States Food and Drug Administration
  - List of countries in which the participant is licensed to do business
  - Provide copies of all relevant permits, approvals, and certificates of insurance, as required by the Program License Agreement
- Provide the list of drug substances for which verification is sought, with lot history dating back two years (if available) of the drug substance(s), manufactured under the current quality system.
- Provide USP with representative sample aliquots of the drug substances, as specified by USP staff.
- Submit the following documentation as described in this manual:
  1. Pre-Audit documentation (see Forms and Checklists, section 20)
  2. Raw material specifications, test results, and raw data relating to the release of material for use (see CMC Documentation Checklist, section 20).
  3. Drug Substance characterization:

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- a. Chemical and physical characterization: structure, crystallinity, state of aggregation, others, as appropriate
  - b. Impurities characterization, including impurities that are process related and that are derived from the raw material used in manufacturing.
4. Toxicology data: submission of toxicology data are not necessary if the drug substance is used in an FDA-approved drug product. If the drug substance is used in a drug product approved for marketing in an "802" country, <sup>1</sup> no toxicology data are necessary. For all other drug substances, toxicology data demonstrating that the article is safe for human use may be required to be included in the submitted documentation. These data may be reviewed by the USP General Toxicology and Medical Device Compatibility Expert Committee.
  5. Drug substance release: specification (physical, chemical and microbiological), test results, and raw data supporting the results for three (3) representative lots.
  6. Stability data.
  7. Drug substance in-line, on-line, and at-line tests when used for release.
  8. Full validation data are not necessary for compendial tests where there is a *USP-NF* monograph. However, data verifying the suitability of the compendial procedure for the participant's drug substance must be included in the package. (See draft General Chapter <1226> *Verification of Compendial Procedures*.) For non-compendial tests, appropriate validation data in compliance with General Chapter <1225> *Validation of Compendial Methods* must be included.
  9. Full validation data in compliance with general chapter <1225> *Validation of Compendial Methods* are required for all tests, when there is no *USP-NF* monograph.

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<sup>1</sup> 802 country: A country that is recognized under section 802(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act and to which a drug or device may be exported, without having the drug or device approved by the U.S. Food and Drug Administration, if the drug or device complies with the laws of that country and has valid marketing authorization by the appropriate authority. These countries include Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and countries within the European Union or European Economic Area (the European Union and the European Free Trade Association) if the drug or device is marketed in that country or is authorized for general marketing in the European Economic Area.

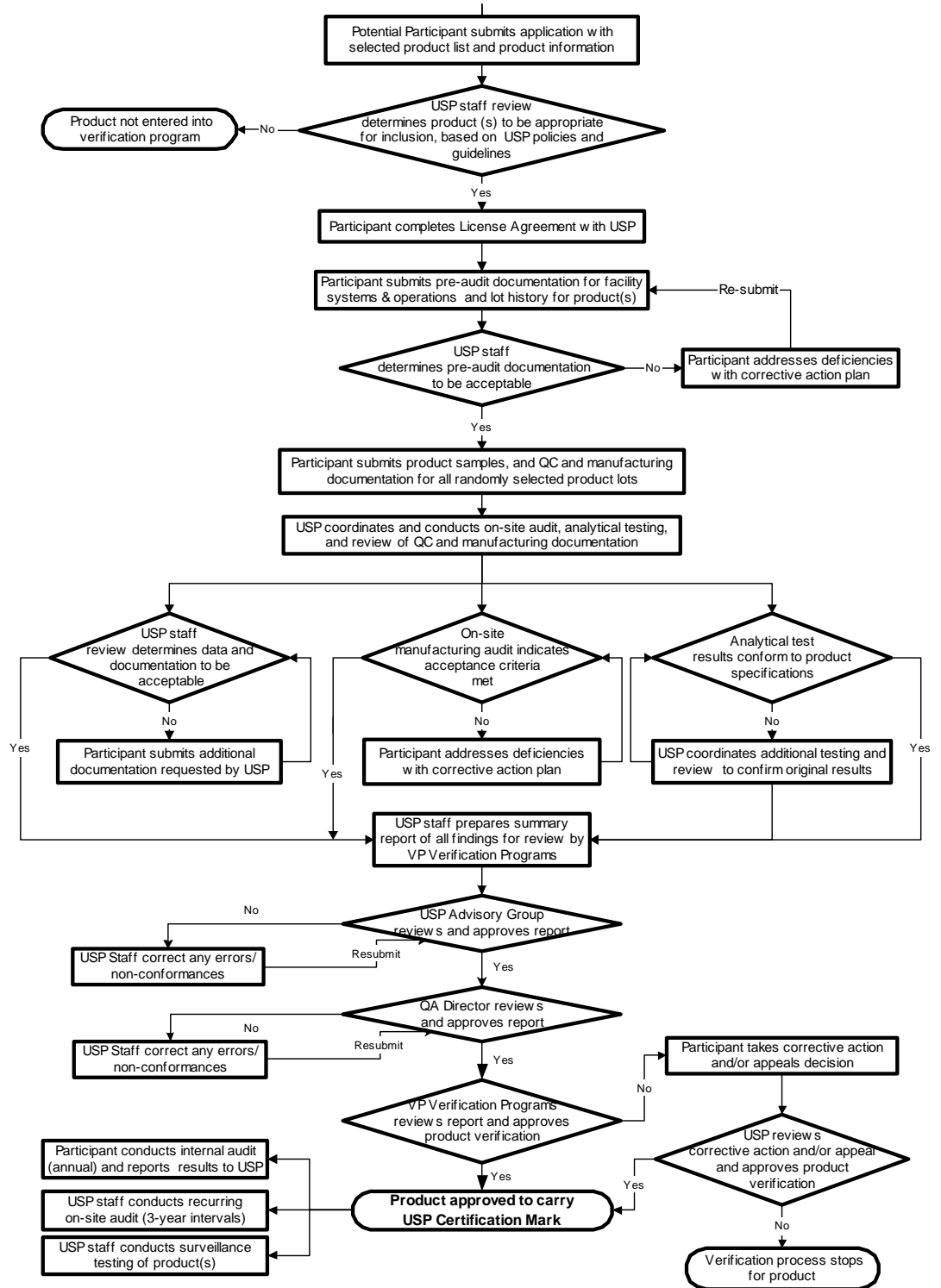
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10. Master batch records.
11. Executed batch records for the three lots of the drug substance(s) under review.
12. Packaging and labeling records for the three lots of the drug substance(s)



4. PROCESS FLOW CHART

Drug Substance VP PROCESS



## 5. DRUG SUBSTANCE ACCEPTANCE CRITERIA

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Upon completion of the license agreement, the participant submits to USP a list of drug substances for which verification is sought. USP staff will review the list of drug substances to confirm that the drug substances are appropriate for inclusion in the program. If so, the participant submits to USP the description of the lot number coding system and the drug substance lot history (lot number, month of manufacture, manufacturing facility, and lot size) for all lots of the drug substances (manufactured during the past year, if available) submitted for verification that have been manufactured under the current quality systems. Also, the participant submits the number of lots recalled, if any, in the past five years for the drug substance(s) under consideration.

Drug substances meeting one or more of the following criteria are eligible for participation in the Program:

- Drug substances that have monographs in the current *USP-NF*
- Drug substances for which monographs have been proposed in *Pharmacopeial Forum (PF)* or are in press for publication in *PF*
- Drug substances for which monographs are under development by the appropriate USP Expert Committee
- Drug substances used in drug products that have been approved for marketing in an 802 country regardless of whether the drug substance is used in a drug product approved for marketing in the United States
- Drug substances used in drug products for which Abbreviated New Drug Applications have been approved by FDA's Office of Generic Drugs but not introduced in the market.
- Drug substances used in drug products for which Abbreviated New Drug Applications have received tentative approval from FDA's Office of Generic Drugs
- Drug substances for which no *USP-NF* monographs exist but are off of patent in the United States
- Drug substances for which no *USP-NF* monographs exist but where there are monographs in the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia*
- Drug substances for which monographs appeared in previous revisions of the *USP-NF* but are not in the current revision and are used in drug products approved for marketing in countries other than the United States
- In certain circumstances drug substances used in drug products approved for marketing in non-802 countries provided toxicology data demonstrating that the article is safe for human use are included in the submitted documentation (See section 3 REQUIRED PROCESS AND SUBMISSIONS)

Drug substances whose monographs have been removed from the *USP-NF* and drug substances that have been banned from use in the United States due to safety concerns of the FDA will not be considered for admission into the Program regardless of whether they are used in legally-marketed drug products in other countries.

## 6. EVALUATION OF PRE-AUDIT DOCUMENTATION

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The Checklist for Pre-Audit Documentation (see Forms and Checklists, section 20) is used in the Program as a tool to ascertain information about the participant, its quality systems, and critical manufacturing information.

The participant should provide the information listed on the Checklist for Pre-Audit Documentation and send it to USP. Upon receipt of the form and accompanying information, USP staff performs preliminary review of the information. If additional information is required, USP staff will inform the participant; such information should be submitted within 40 calendar days after receipt of notice from USP staff.

**Note that the requested information must be submitted in the format indicated on the Checklist for Pre-Audit Documentation. The requested information must be submitted in a three-ring binder. Complete documentation must be received before the review process can begin.**

If the participant has prepared a Drug Master File (DMF) or similar document for submission to regulatory agencies, the Program may accept it in lieu of the Quality Control information. This document should address the key elements listed in this section. As above, USP staff will inform the participant if additional information is required.

In evaluating the Checklist for Pre-Audit Documentation, the absence of any of the following listed elements will be determined as deficiencies that will exclude the participant's drug substance from consideration for verification until the deficiencies are corrected.

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- Flow chart(s) of process (es)
- Site map/layout
- Organizational chart including all key manufacturing and QA/QC personnel
- Qualifications of key personnel
- Training program
- Table of contents from manufacturing, laboratory, QA, and QC SOP manuals
- Receiving and material handling SOPs
- Document management policy and SOPs
- List of process equipment requiring calibration, preventive maintenance, and cleaning
- Program for calibration and preventive maintenance for process equipment
- Program for process validation
- Labeling management policy and SOPs
- Deviation policy and SOPs
- Laboratory control policy and SOPs
- Sample tracking system
- Stability program
- Starting chemical or raw material supplier verification program
- Contract laboratory verification program (if applicable)
- Complaint handling/recall policy and SOPs

In certain cases, the participant may not have a formally established program for all aspects of the quality systems. If so, the participant can provide a description of their informal process along with a proposed plan and schedule to formalize it.

Deficiencies, if any, will be noted and provided to the participant. The participant should develop corrective action plans within 30 calendar days of receipt of the notification. USP will respond to the proposed action plans within 30 calendar days of receipt. If the plan is acceptable, corrective actions must be implemented within six calendar months of receipt of USP's decision. If the information on the corrective action is found acceptable by USP, it will proceed with the verification process. If the participant fails to develop and implement corrective action, the verification process will be discontinued.

## 7. **SAMPLING AND SUBMISSION OF DRUG SUBSTANCE DOCUMENTATION**

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For each drug substance for which a participant is seeking verification, USP will select the lot(s) to be used in the verification process. This decision will be based in part on the lot history for the drug substances and the availability of the drug substance lots for sampling. The lots selected will be from those manufactured at regular commercial scale. No lots manufactured under pilot scale or research and development scale will be accepted.

USP will select, at a minimum, three drug substance lots for each drug substance for which verification is being sought.

Sample aliquots from the selected lots will be collected during the facility audit and shipped by Program representatives to the appropriate laboratory. Alternatively, USP may request that the participant obtain representative sample aliquots of the drug substance lot(s) and ship them via the most expedient and appropriate courier services to USP.

Drug substances submitted to the Program should be sampled according to the participant's approved sampling plan and packaged either in the commercial packaging or in a suitable (e.g., similar, more portable, biocompatible) container closure system. The container needs to be labeled, at a minimum, with the following information:

- Participant's Name
- Drug Substance Name
- Drug Substance Item Code Number
- Drug Substance Lot Number
- Date Sampled
- Sampler's Initials
- Quantity of Drug Substance

The participant must submit the following documentation for the chosen lot(s).

1. Chemistry and Manufacturing Controls (CMC) Documentation Checklist

**Note that the requested information must be submitted in the format indicated on the Chemistry and Manufacturing Controls (CMC) Documentation Checklist (see Forms and Checklists, section 20). The requested information must be submitted in a three-ring binder. Complete documentation must be received before the review process can begin.**

## 8. EVALUATION OF QUALITY CONTROL DOCUMENTATION

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USP will review all quality control documentation submitted (See Chemistry and Manufacturing Controls (CMC) Documentation for Drug Substances, Dietary Ingredients, or Excipients, under Forms and Checklists, section 20) for drug substances accepted into the Program. USP will determine whether the specifications (tests, analytical procedures, and acceptance criteria) provided are sufficient to demonstrate consistent and appropriate drug substance quality. USP will review specifications relating to raw materials, in-process and/or intermediate materials and drug substances, packaging and labeling materials, reference materials, analytical validation data, stability data, as well as the certificate of analysis and analytical data from the selected lots.

**Note that the requested information must be submitted in the format indicated on the Chemistry and Manufacturing Controls (CMC) Documentation for Drug Substances, Dietary Ingredients, or Excipients (see Forms and Checklists, section 20). The requested information must be submitted in a three-ring binder. Complete documentation must be received before the review process can begin.**

**Raw Materials, Critical/Key Intermediates and Drug Substance(s):** For drug substances for which *USP-NF* monographs exist, USP will verify conformance to the requirements specified in the monograph.

For drug substances for which there are no compendial monographs, USP will verify that the specifications provided by the participant are adequate to ensure the identification, strength, quality, and purity, in accordance with the labeling. The specifications will be evaluated, as applicable, for:

- Identification
- Content of specific entity or marker(s).
- Foreign substances and impurities
  - Heavy metals.
  - Residual solvents/organic volatile impurities.
  - Known toxic and other impurities.
  - Microbial contaminants.
- Physicochemical properties (e.g., water, pH, melting point, optical rotation, etc.)

For critical/key intermediates, USP will verify that the specifications provided by the participant are adequate to ensure the drug substance meets its specification.

Where necessary, USP may test either all or some of the key intermediates, where these key intermediates are isolated and tested, involved in the manufacture of drug substances under

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verification in accordance with compendial specifications (if applicable) or the specifications provided by the participant.

For critical/key intermediates purchased from contract manufacturers, participants must have a vendor qualification program in place. In general, USP will not subject these intermediates to additional testing except when the penultimate intermediate is purchased.

Please refer to section 11 SPECIFICATIONS FOR RAW MATERIAL AND/OR DRUG SUBSTANCE for further details on material specifications.

Applicable sections of the checklist include 1.1 Nomenclature; 1.2 Structure; 1.3 General Properties; 2.3 Control of Materials; 2.4 Controls of Critical Steps and Intermediates; 3.1 Elucidation of Structure and Other Characteristics; 3.2 Impurities; 4.1 Specifications; and 4.5 Justification of Specification.

**Packaging and Labeling Materials:** USP will review descriptions and specifications provided by the participant for packaging materials that are or will be in direct contact with the drug substance (primary packaging materials) and secondary packaging materials, as well as samples and specifications provided for labels and labeling materials.

Reference to the *USP–NF*, other pharmacopeias, and other standards on labels or labeling must be completely accurate. Labeling must comply with all applicable regulatory and compendial labeling requirements.

Applicable sections of the checklist include 1.1 Nomenclature; and 6.0 Container Closure System.

**Method Validation:** USP will review documentation for each analytical procedure. If the analytical procedure is found in an official compendium, there is no need for a complete validation report. In this case, the suitability of the procedure for testing the specific drug substance must be supported by analytical data. (See General Chapter <1226> *Verification of Compendial Procedures*.) If the analytical procedure is not in an official compendium, the procedure must be validated according to the *USP–NF* General Chapter <1225> *Validation of Compendial Methods*, and/or ICH Q2A Text on Validation of Analytical Procedures and Q2B Validation of Analytical Procedures: Methodology.

If the validation data provided by the participant do not demonstrate that the procedure is suitable for its intended use the process will stop until adequate validation data are provided.

Applicable sections of the checklist include 4.2 Analytical Procedures; and 4.3 Validation of Analytical Procedures

**Reference Materials:** For official USP Reference Standards that have been used for their intended purpose, all that is needed is an indication of the lot number of the official USP Reference Standard used. For non-USP reference standards or for unintended uses of USP Reference Standards, the source of the material and data to support the suitability of the material for its intended use must be submitted.

Applicable sections of the checklist include 5.0 Reference Standards or Materials.

**Stability Data:** Procedures used in stability studies will be reviewed to determine if they are suitable for evaluating drug substance quality attributes such as appearance, content, degradation products, aggregation, and microbial counts that are susceptible to change during storage and likely to influence the drug substance's quality and performance. Data for review include the following:

- Real-time stability studies
- If real time stability studies are not available at the time of verification, then accelerated stability data may be acceptable provided the participant follows-up with submission of real time stability data as they become available.
- Applicable sections of the checklist include 7.1 Stability Summary and Conclusions; 7.2 Post-approval Stability Protocol and Stability Commitment; and Stability Data.

**Certificate of Analysis:** USP will evaluate data and verify that the analytical results on the certificates of analysis, from the selected drug substance lots under review, are in compliance with the specification proposed by the participant. In case of non-compliance, USP will provide recommendations for changes.

Applicable sections of the checklist include 4.4 Batch Analysis.

**Request for Supplemental Information:** If the quality control documentation is found unacceptable, incomplete, not in the requested format, or inadequate for any reason, USP may return it to the participant for revision and resubmission.

If the quality control documentation is considered unacceptable and USP determines, after discussion with the participant, that the evaluation of additional information or drug substance samples submitted by the participant will not add useful data, the entire quality control documentation will be deemed unacceptable and the verification process will be discontinued.

If the quality control documentation is considered unacceptable but, based on discussions with the participant, there is sufficient cause for USP to confirm any supplied procedures and/or analytical results, the drug substance samples submitted by the participant will be analyzed either in USP laboratories or in USP approved contract laboratories. If the laboratory results support the acceptance of the quality control documentation, USP will proceed to the next step in the verification process. If the laboratory results support the acceptance of the quality control documentation, but lead to other issues, a written report will be sent to the participant asking for



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comments and additional information. If the laboratory results do not support the acceptance of the quality control documentation, the verification process will be discontinued.

**Drug Master File (DMF):** If the participant has a prepared DMF or similar document for submission to regulatory agencies, USP may accept it in lieu of the Quality Control information. This document should address the key elements listed in this section. As above, USP staff will inform the participant if additional information is required.

## 9. EVALUATION OF MANUFACTURING DOCUMENTATION

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USP will review all manufacturing documentation (submitted per Chemistry and Manufacturing Controls (CMC) Documentation Checklist for Drug Substances, Dietary Ingredients, or Excipients, under Forms and Checklists, section 20) for drug substances accepted into the Program.

**Note that the requested information must be submitted in the format indicated on the Chemistry and Manufacturing Controls (CMC) Documentation for Drug Substances, Dietary Ingredients, or Excipients. The requested information must be submitted in a three-ring binder. Complete documentation must be received before the review process can begin.**

The documentation submitted must include:

- Master formulas/manufacturing directions/manufacturing guide.
- A process diagram of chemical synthesis, extraction, secondary/tertiary recovery, fermentation, grinding, sifting, sizing, cleaning, etc., if applicable.
- Acceptable procedures for reprocessing which have demonstrated that the lot meets label or certificate of analysis declaration and the stability specification. Alternatively, a statement that reprocessing is not performed would suffice.
- Identification of steps requiring a quality control check (particularly critical/key intermediate steps involved in synthesis, extractions, sizing, etc.).
- Executed batch records for lots that USP has selected for review.

The batch records must include:

- Manufacturing instructions.
- Packaging instructions.
- Release data related to the quality control for all critical/key intermediates involved in the manufacture of the drug substance undergoing verification.
- Labeling for the subject lot.
- Indication of QA final release approval.

**In-process Monitoring:** USP will review specifications provided by the participant for in-process control steps defined in the internal manufacturing and process directions.

Applicable sections of the checklist include 2.1 Manufactures(s); 2.2 Description of Manufacturing Process and Process Controls; 2.2.1 Alternate Processes; 4.4 Batch Analysis; and 8.0 Facilities and Equipment.

**Manufacturing Process Validation:** USP will review the developmental history of the manufacturing process and process validation studies for the drug substance.

Applicable sections of the checklist include 2.5 Process Validation and/or Evaluation; and 2.6 Manufacturing Process Development.

**Other Requirements:** USP will review information assessing the risk with respect to potential contamination with adventitious agents, when necessary. If the drug substance contains any additives, the chemistry and manufacturing controls for the additive will be reviewed by USP. Lastly, any information specific to a particular region will be reviewed according to the appropriate regional guidance and/or regulatory requirements.

**Applicable sections of the checklist include 9.0 Adventitious Agents Safety Evaluation; 10.0 Excipients; and 11.0 Regional Information.**

## 10. TESTING OF DRUG SUBSTANCE SAMPLES

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Testing of drug substance samples will begin after USP has determined that the quality control documentation and manufacturing documentation for the drug substance is complete and acceptable.

Drug substances will be tested for critical quality attributes as determined by USP to evaluate the quality of the drug substance and demonstrate conformance with the label claims and certificate of analysis.

Please refer to section 11 SPECIFICATIONS FOR RAW MATERIAL AND/OR DRUG SUBSTANCE for further details on testing of drug substance samples.

USP will coordinate testing of drug substance samples in USP laboratories and/or by one or more approved contract laboratories. A single analysis will be performed for each drug substance test. Test data will then be evaluated for accuracy and to determine if the drug substance conforms to the acceptance criteria provided by the participant.

If the test data obtained conform to the acceptance criteria and there are no other issues arising from the test results, USP will proceed to the next step in the verification process.

If the test data obtained do not conform to the acceptance criteria or if there are other issues arising from the test results, USP will reevaluate the raw data submitted by the laboratory to confirm the accuracy of test results. If specific analytical errors are found, a sample retest will be requested from the laboratory. The laboratory will be requested to reanalyze the original sample, if possible, in duplicate. If the reanalyzed results agree with the initial test result, all results will be averaged and reported. If the reanalyzed results confirm the suspected analytical error, only the reanalyzed results will be averaged and reported.

In the case of nonconforming results, where there is no determinant error, the laboratory will be requested to reanalyze the original sample, if possible, in duplicate, along with a newly submitted sample of the drug substance lot, in duplicate. Testing on each sample set will be performed by different experienced analysts. If the four reanalyzed results disagree with the initial test result, the average of the four reanalyzed test results will be reported. If the four reanalyzed results agree with the initial test result, all results will be averaged and reported.

In all cases, the reported results will be compared to the participant's acceptance criteria for determining compliance to label and/or certificate of analysis claim(s). In the event of a question regarding compliance to the participant's acceptance criteria, label, and/or certificate of analysis claim(s), the decision by USP shall be final.

**11. SPECIFICATIONS FOR RAW MATERIAL AND/OR DRUG SUBSTANCE**

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A specification is defined as the list of tests, analytical procedures, and acceptance criteria that define the standard of quality for a material. The acceptance criteria may be numerical limits, ranges, or other criteria for the given test procedure. The specification establishes the set of criteria to which a raw material and/or drug substance should conform in order to be considered acceptable for its intended use. The specification is chosen to confirm the quality of the material rather than to establish full characterization, and should focus on those characteristics that ensure the safety and suitability of the material for its intended use.

The quality of the drug substance is determined, in part, by the in-process controls applied throughout manufacture, and may involve key intermediates for which specifications are given. In some cases, a drug substance may have more restrictive acceptance criteria for release than for the shelf-life or retest date of the drug substance in order to ensure that the drug substance will remain within its acceptance criteria throughout its shelf-life or retest date. Specifications for key intermediates, release, and shelf-life of the drug substance will be reviewed by USP staff.

As previously indicated, for a drug substance for which a compendial monograph exists, USP will verify conformance to the requirements specified in the monograph.

For drug substances for which there are no *USP-NF* monographs, USP will evaluate whether the specifications provided by the participant are adequate to ensure identification, strength, and quality, in accordance with the ICH Q7 guideline

The following tests are considered generally applicable to drug substances.

- (1) Description: a qualitative statement about the state (e.g., solid, liquid) and visual characteristics (e.g., color) of the drug substance.
- (2) Identification: identification testing should be unequivocal and should be able to discriminate between materials of closely related structure, which are likely to be present.
- (3) Assay: a specific, stability-indicating procedure should be included to determine the content of the drug substance. If a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity.
- (4) Foreign Substances and Impurities: tests should be provided for the presence of foreign substances and impurities, to limit such substances to amounts that are unobjectionable under the conditions in which the drug substance is to be employed. Foreign substances and impurities can arise from raw materials, the manufacturing process, and from the degradation of

the drug substance. Appropriate criteria should be stated for each individual impurity and may include both identified and unidentified impurities.

(a) Organic impurities: in some cases, it is possible to use the same procedure (e.g., HPLC) for both assay of the drug substance and quantitation of the organic impurities.

(b) Inorganic impurities: procedures and acceptance criteria for inorganic impurities should be based on knowledge of the manufacturing process and may be determined by non-specific tests (e.g., sulfated ash, residue on ignition) or by specific tests (e.g., atomic absorption spectroscopy).

(c) Residual solvents: residual solvents are organic volatile chemicals that are used or produced in the manufacture of the drug substance, and which are not completely removed by practical manufacturing techniques. Procedures such as those delineated in the USP general chapter <467> *Residual Solvents* should be employed, and the content of solvents in the drug substance should be evaluated and justified.

(5) Physicochemical properties: the physical nature of the drug substance may involve properties such as pH of an aqueous solution, melting point/range, and refractive index, depending on its intended use.

(6) Particle size: for drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on the drug product's dissolution rate, bioavailability, and/or stability, in which case an appropriate procedure for measuring particle size distribution and corresponding acceptance criteria should be provided.

(7) Polymorphic forms: many drug substances exist in different crystalline forms which differ in their physical properties. Polymorphism also may include solvation or hydration products (pseudopolymorphs) and amorphous forms. In cases, where differences exist that can affect the performance, bioavailability, and/or stability of the drug product, then the appropriate solid state of the drug substance should be specified, and the appropriate physicochemical procedures used to determine which form(s) exist.

(8) Water content: this test is important in cases where the drug substance is known to be hygroscopic or degraded by moisture. In some cases, a Loss on Drying procedure may be considered adequate; however, a procedure that is specific for water (e.g., Karl Fischer titration) is preferred.

(9) Pesticides: For articles of botanical origin pesticides testing should be conducted according to USP <561> *Articles of Botanical Origin* and should comply with the applicable Federal regulations in the United States, or with the requirements of other appropriate government bodies.

(10) Undesirable Contaminants: Material of animal origin should be monitored for the potential presence of bovine spongiform encephalopathy (BSE) or transmissible spongiform encephalopathy (TSE) material. In these cases, one should consult *European Pharmacopoeia*

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(EP) General Chapter 5.2.8 "Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products"; and the U.S. Department of Agriculture, Animal and Plant Health Inspection Service (APHIS), Federal Register: November 4, 2003, Volume 68, Number 213 (Proposed Rules) 9 CFR Parts 93, 94, and 95, Bovine Spongiform Encephalopathy; Minimal Risk Regions and Importation of Commodities. Also, material of plant and animal origin should be monitored for the potential presence of genetically modified organisms (GMO) material.

(11) Microbial Limits: There may be a need to specify the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella spp.*, *Pseudomonas aeruginosa*). These microbes should be suitably determined using pharmacopeial procedures (e.g., <61> *Microbial Limit Tests*).

For questions or clarification regarding specifications for raw materials and/or drug substances, please contact Program staff at 301-881-0666.

**12. ON-SITE AUDIT CRITERIA**

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USP staff auditors and/or approved contract auditors perform the on-site audit of the participant's facilities and operations. The on-site audit will be conducted at least once every three years. In general, participants will conduct internal audits on an annual basis after successfully completing all aspects of the Program. In its sole discretion, USP may conduct additional on-site audits on a for-cause basis, in response to a major change, or as a follow up to the initial audit when Action Level 1 deficiencies were noted, see sections 13 USP DRUG SUBSTANCE VP REPORT OF FINDINGS and 16 PARTICIPANT'S INTERNAL AUDITS, USP AUDITS, AND ANNUAL REPORTS.

In USP's sole discretion the audit may be performed unannounced or with notice at a date and time mutually agreed upon by USP and the participant. Whether the audit is announced or unannounced is within USP's complete discretion. For scheduled audits, USP will communicate to the participants' designated contact person the agenda for the audit specifying all relevant areas to be covered. The participant must assure the availability of the required personnel. Whether announced or unannounced, the Q7 guideline principles will be followed. Safety procedures for the areas being audited will be followed.

The auditors will evaluate the findings of the on-site audit, using the ICH Q7 *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* as guidance.

Auditors will apply the following criteria: (Please See Forms and Checklists, section 20 for complete list)

**Quality Management**

- Dedicated Quality Assurance/Quality Control department.
- System to ensure drug substance quality prior to release.

**Organization/Personnel**

- Adequate number of qualified employees.
- Training program for the competency of all employees.

**Facilities/ Equipment**

- Adequate security to prevent access for unauthorized personnel.
- Adequate size and design of facility.
- Maintenance and calibration of equipment to ensure consistent performance for its intended use.
- Documentation of use, calibration, cleaning, and preventive maintenance of equipment.
- Electronic records, computerized systems, including proof of performance, appropriate security and backup.



### **Document Management**

- Procedures for control of Standard Operating Procedures (SOPs), lot records, analytical procedures, and specifications that include required approvals and revision/archival control, where appropriate.

### **Materials Management**

- Program for receipt, quarantine, disposition, release, retain, and distribution of incoming materials. Sample tracking from receiving through analysis in the laboratory.
- System of material reconciliation.

### **Production and In-process Controls**

- Adequate controls for raw material weighing, measuring and verifying.
- Designation of all raw materials, manufactured intermediates, and finished drug substances as to their status.
- SOPs for monitoring, sampling, documenting all production activities.
- Adequate procedures to prevent cross contamination.

### **Label Control**

- Program for controlling label revision.
- Program for monitoring and use of incoming labels.
- Assurance of accountability of labels.
- Monitoring of regulations as required.

### **Laboratory Controls**

- Written analytical procedures and acceptance criteria.
- Use of compendial procedures where applicable.
- Use of validated/qualified and appropriate test procedures.
- Review of data and analysts' qualifications.
- Monitoring/tracking of media/reagents prior to use.
- Appropriate maintenance and calibration of laboratory equipment/instruments.
- Out of specification (OOS) policy and procedures

### **Stability**

- Program to evaluate drug substance stability.
- Testing within defined time frames.
- Formal program for resolution of discrepancies in testing.
- Data to support retest date of drug substances submitted to the Program for verification.

**Process Validation**

- Demonstrated for drug substances submitted to the Program for verification.

**Change Control**

- Formal change control system to determine if change affects product quality
- SOP for investigating and analyzing non-conforming results and trends.
- Written procedures to document changes.
- System to ensure drug substance quality prior to release

The on-site audit will be conducted according to the On-Site Audit Checklist (See Forms and Checklists, section 20). Upon completion of the on-site audit, USP will evaluate the on-site audit findings and summarize them in an audit report, which will include a list of any deficiencies. The audit report will then be forwarded to the participant along with the Program's report of any actions that the participant needs to take to correct these deficiencies. The participant will have 40 calendar days to reply to reported deficiencies with a corrective action plan. Failure to do so may result in the discontinuation of the verification process. For Action Level 1 deficiencies (see section 13 USP DRUG SUBSTANCE VP REPORT OF FINDINGS) proof of corrective action, with the date of completion or progress made, must be submitted to USP before the verification process can continue for the drug substance. A follow up on-site audit may be necessary before the verification process can continue. For Action Level 2 deficiencies, the verification process will continue, but deficiencies must be addressed and corrective action taken before the verification letter can be issued for the drug substance. For Action Level 3 deficiencies proof of corrective action, with the date of completion or progress made, must be submitted to USP with the participant's first annual report.

**13. USP DRUG SUBSTANCE VP REPORT OF FINDINGS**

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A report will be issued to participants listing the final determination and status of any issues regarding the various elements of the Program as it pertains to the participant. The report for each manufacturing site will be segregated according to the following elements of the program, as applicable:

- Pre-Audit Documentation
- On-Site Audit
- Quality Control Documentation for all intermediates and finished drug substance
- Manufacturing Documentation
- Analytical Results at all stages of manufacture

The results for the Pre-Audit Documentation and the On-Site Audit apply to the manufacturing site audited and the drug substances manufactured at that site, whereas the results for the remaining section(s) will be drug substance specific.

The status of the issues or deficiencies within each program element may be divided into three categories: Action Level 1, Action Level 2, and Action Level 3. These three categories differ according to the nature and potential impact of the issue or deficiency. All Action Levels require some action to be taken by the participant.

**ACTION LEVEL 1** issues involve a lack of a quality system program element, a lack of essential drug substance criteria, or drug substances identified as having critical deficiencies. Action Level 1 issues may be resolved by supplying essential information or by making major changes to a drug substance or process. Action Level 1 issues involve changes to the current quality system. Action Level 1 issues must be adequately resolved before the verification process can continue for the drug substance, and may require that the drug substance be resubmitted for verification. A follow up on-site audit may be necessary.

**ACTION LEVEL 2** issues involve a lack of information regarding a quality system program element, a lack of significant drug substance criteria, or drug substances identified as having major deficiencies. Action Level 2 issues can be resolved by supplying supplemental information or by making minor changes to the drug substance or process. Action Level 2 issues do not involve changes to the current quality system. The verification process can continue pending resolution of Action Level 2 issues, but such issues must be adequately resolved before the verification letter can be issued for the drug substance.

**ACTION LEVEL 3** issues involve the need for clarifying information or newly requested information regarding a quality system program element, requested improvements to drug substance criteria, or drug substances identified as having

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minor deficiencies. Action Level 3 issues can be resolved by supplying additional information or by making requested changes to the drug substance or process. Action Level 3 issues would allow the USP verification to be issued subject to the firm's commitment to address the issues cited within the specified time period. Failure to address an Action Level 3 issue in a timely manner could lead to revocation of verification status.

The status of each category (Pre-Audit Documentation, On-Site Audit, and Drug Substances) is indicated by an overall assessment of Pass or Fail, depending on the nature of the issues/deficiencies within each category. The grading system of Pass or Fail is based on the following determination:

**PASS** indicates that only Action Level 3 issues or deficiencies need to be resolved. Verification would be considered without further process, and will be reconsidered based on USP follow-up or the participant's first self-audit report.

**FAIL** indicates that one or more Action Level 1 or Action Level 2 issues or deficiencies need to be resolved. The participant would need to make the appropriate change(s) to the drug substance or process and most likely will need to resubmit the drug substance for verification.

## 14. **ISSUANCE AND USE OF THE USP CERTIFICATION MARK**

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On satisfactory completion of the:

- Evaluation of pre-audit documentation
- Evaluation of on-site audit report
- Evaluation of quality control documentation
- Evaluation of manufacturing documentation
- Testing of drug substance samples

For each ingredient that successfully completes the Verification Program, USP will issue a Certificate of Standards Compliance. The Certificate will specify which of the participant's drug substance(s) are entitled to the use of the USP Pharmaceutical Ingredient Certification Mark and other limiting information (such as manufacturing site information) as appropriate.

USP will review all labeling that will include the USP Pharmaceutical Ingredient Certification Mark for the prospective drug substance. USP reserves the right to ask for additional documentation as necessary.

The mark must be used in accordance with the guidelines in the USP Drug Substance VP Certification Mark Usage Manual and the Program License Agreement, which will be provided by USP along with the notification of approval to use the mark. These guidelines relate to:

- Size and color of the Certification Mark.
- Acceptable format and materials.
- Specifications for reproduction.
- Examples of appropriate and inappropriate use.
- Acceptable and unacceptable usage of the Certification mark in advertising and promotional materials, exhibit signage, speaking engagements, presentations, educational materials and events, and on websites.

USP requires submission of artwork for drug substance labels, advertising, promotional, or other materials that include the Certification Mark for pre-approval. The artwork must be submitted in final mock-up form in color along with stock (paper) samples and bindery details, if applicable. A specification sheet outlining the strategy/goals of the materials, the target audience, and the number of pieces—if any—to be mailed must be provided along with the artwork. USP also may require actual production copies of artwork using the mark to be submitted for evaluation.

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Written approval or disapproval of the materials submitted will be provided by USP to the participant within 10 calendar days. USP may, if necessary, request additional materials from the participant. Materials must be in conformance with the recommended guidelines to be approved by USP. If the materials are not approved by USP, USP will notify the participant in writing. The participant will be given an opportunity to correct or adjust deficiencies and resubmit the materials to USP. The participant must obtain USP's final written approval before using the mark.

News releases and associated references to the Program must be submitted to USP for approval prior to release. If desired, USP, in its discretion, also will work with the participant on joint news releases. USP will draft, edit, and coordinate approvals of the joint news releases and work with the participant to determine the media list(s) for distribution.

A list of licensed participants and licensed drug substances under the Program will be made available to the public on the USP website.

If the Certification Mark is misused or improperly used, USP will work with the participant licensed to use the Certification Mark to resolve the problem(s) or any related dispute(s). USP and the licensed user will agree on a written plan to bring the usage into required conformance. However, if the problem cannot be resolved to USP's satisfaction, USP will issue a written warning of proposed revocation or suspension of the license to use the Certification Mark either in its entirety or on a drug substance specific basis. The warning shall specify the steps required for the participant to come into conformance and avoid revocation or suspension, and a reasonable time period for achieving conformance. In the case of continued non-conformance, USP will make a final decision to revoke or suspend the participant's license to use the Certification Mark, either in its entirety or on a drug substance specific basis. Such a decision may not be appealed by the participant.

Participants are reminded, however, that the terms and conditions set forth in the Program License Agreement have precedence over this manual.

**15. NEED FOR RE-EVALUATION AND RENEWAL OF VERIFICATION**

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After USP has granted approval to use the Certification Mark, any major changes to a drug substance's specification, process control, raw material source, equipment, manufacturing site, testing, or any other criteria deemed by the participant to be essential or significant, must be reported in writing to USP.

A **Major change** is defined as a change that has a substantial potential to have an adverse effect on the identification, strength, quality, and purity of a drug substance as they may relate to the safety or intended use of the drug substance. A major change requires notification to USP and approval by USP prior to implementation. Such notification by the participant must be made in writing with a list of the drug substances that are affected by such changes, the details of the changes, and the rationale for the changes. This type of submission of supplemental information will be classified as a PRIOR APPROVAL NOTIFICATION. Such notification shall be clearly marked Prior Approval Notification by the participant. The notification must include data from three (3) lots manufactured prior to the change and three (3) lots manufactured post change. Upon receipt of such notification USP will expedite the review of such notification and communicate its decision.

A **Moderate change** is a change that has moderate potential to have an adverse effect on the identification, strength, quality, and purity of the drug substance as they may relate to the safety or intended use of the drug substance. Moderate changes must be communicated by the participant to USP at the time the change is introduced; pre-notification is not required.

A **Minor change** is a change that has minimal potential to have an adverse effect on the identification, strength, quality, and purity as they may relate to the safety and the intended use of the drug substance. Such changes must be communicated by the participant in its Annual Report.

## MAJOR CHANGES

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identification, strength, quality, and purity of a product as they may relate to the safety or intended use of the drug substance. These examples are illustrative and do not represent an exhaustive list.

### Manufacturing sites:

1. A move to a different manufacturing site, except one used to manufacture or process an intermediate in the manufacture of the drug substance, when the new manufacturing site has never been audited by the USP for the type of operation that is being moved or the move results in a restart at the manufacturing site of a type of operation that has been discontinued for more than two years.
2. A move to a different manufacturing site when the manufacturing site has not been audited by USP for the type of operation being moved.

### Manufacturing process:

1. Change in the route of synthesis of the drug substance.
2. Change from one type of drying process to another (e.g., oven tray, fluid bed dryer, microwave).
3. Changes in solvent used in the manufacturing process.
4. Changes in filtration techniques (e.g., filtration through filter paper to centrifugation or vice versa).
5. Any process change made after the final intermediate processing step in the drug substance manufacture.
6. Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile<sup>2</sup> and/or its physical, chemical, or biological properties.

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<sup>2</sup> CDER *Guidance for Industry BACPAC 1: Intermediates in Drug Substance Synthesis Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation* (Guidance was withdrawn by CDER June 2006)—Equivalence of impurity profiles is shown by tabulating the data for pre-change and post-change lots. While this guidance generally applies to changes prior to the final intermediate, the principles will be applied by the Program to the drug substance as well. If the following conditions are met there has been no significant change in the impurity profile.

1. Each existing impurity is within its acceptance criterion or, if not stated, is at or below the upper statistical limit of historical data.
2. Total impurities are within the stated acceptance criterion or, if not stated, are at or below the upper statistical limit of historical data.
3. Each existing residual solvent if within its acceptance criterion or, if not stated, is at or below the upper statistical limit of historical data.
4. New residual solvents, in either an intermediate or the drug substance, are at or below the levels recommended in the ICH guidance *Q3C Impurities: Residual Solvents*.  
In addition, the following are applicable to drug substances under the USP Drug Substance VP:
5. No new impurity is present at or above 0.1% nor has an impurity previously in the impurity profile at this level disappeared.
6. Residual solvent and impurities remain within 3 standard deviations of the mean of the lots produced before the change.
7. All impurities are at or below the mean plus 3 standard deviations of the lot produced before the change.



7. For natural products, such as drug substances derived from fermentation processes, changes in source material (e.g., microorganism, plant material) or change in solvent(s).
8. Changes in scale of manufacturing, namely batch size increase or decrease in excess of ten-fold in either direction.
9. Change in the production vessel's design and services, such as chilled water, hot water, and stirrers, connected to the vessel.
10. Change in the type of vessel used in the production. For example, change from glass-lined reactors to a stainless steel vessel.
11. Change in sourcing, specification, and/or vendor for raw material.
12. Change in the type of antioxidant or preservative used in liquid or semisolid drug substances.

**Specifications:**

For purposes of defining specifications, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described.

1. Relaxing an acceptance criterion or deleting any part of a specification.
2. Adoption of a new analytical procedure without sufficient rationale for testing raw materials, intermediates, and/or the drug substance. An example of this type is a change in the analytical procedure employing high-pressure liquid chromatography to one employing spectrophotometry or titration.
3. Any change in the analytical procedures for the drug substance or raw materials and intermediates, other than editorial.
4. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components.

**Packaging:**

1. For liquid and semisolid drug substances, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components.
2. For liquid and semisolid drug substances in a permeable or semipermeable container closure system, a change to an ink and/or adhesive used on the permeable or semipermeable packaging component.
3. Deletion of a secondary packaging component intended to provide additional protection to the drug substance (e.g., carton to protect the contents from light, overwrap to limit transmission of moisture or gases).
4. A change to a new container closure system, if the new container closure system does not provide the same or better protective properties than the one used at the time of entering the Program.
5. A change in the dimension of the container closure system such as shape or size.
6. A change in or addition or deletion of a desiccant.
7. A change in the lining material inside the drums.

**Labeling:**

1. Change in the labeled storage conditions.
2. Increase in length of the expiration date/retest date.
3. Claims of superiority to the same drug substance manufactured by another participant; such claims should not be on labeling.

**MODERATE CHANGES**

The following are illustrative examples of moderate changes and do not represent an exhaustive list.

**Manufacturing sites:**

1. A move to a different manufacturing site for testing, if the new testing facility has the capability to perform the intended testing.
2. A move to a different manufacturing site for the manufacture or processing of an intermediate involved in the manufacture of the drug substance.

**Manufacturing process:**

1. Replacement of equipment with that of a similar but not identical design and operating principle that does not affect the process.
2. A change in production control or analytical procedure that provides an increased assurance that the drug substance will have the characteristics of identification, strength, quality, and purity that it purports to have.
3. Any change in the scale of operation of an intermediate (batch size increase or decrease) that involves a different type of equipment for manufacturing.

**Specifications:**

1. Relaxing an acceptance criterion or deleting a test for raw materials used in the drug substance manufacturing or in-process materials prior to the penultimate intermediate.
2. An addition to a specification that provides increased assurance that the final drug substance submitted for verification will have the characteristics of identification, strength, quality, and purity that it purports or represents to possess.
3. A change in the analytical procedure used for testing components, packaging components, or the penultimate stage intermediate or starting materials that provides the same or increased assurance of the identification, strength, quality, and purity of the material being tested.

**Packaging:**

1. Changes in packaging materials to control odor (e.g., charcoal packets).

**Labeling:**

1. Changes to any cautionary statement on labels and/or labeling, such as handling instructions, except those required under federal, state, or local, and other applicable regulatory requirements.
2. Decrease in the length of expiry.

**MINOR CHANGES**

The following are illustrative examples of minor changes and do not represent an exhaustive list:

**Manufacturing sites:**

1. A move to a different manufacturing site, already audited by USP, for secondary packaging.
2. A move to a different manufacturing site, already audited by USP, for labeling.

**Manufacturing process:**

1. A change in the vessel used for manufacturing involving replacement of the old vessel with a new one of the same construction material and size.

**Specifications:**

1. Any change in the specification made to comply with changes in an official compendium (e.g., *USP-NF*).
2. Tightening of acceptance criteria for the raw materials, intermediates, and drug substance.

**Packaging:**

The following changes in the container closure system are considered minor provided the new package system provides the same or better protective properties (e.g., protection from light, moisture):

1. Changing from metal screw cap to plastic screw cap or vice versa.
2. Changing from one plastic container (primary and/or secondary) to another of the same type of plastic (e.g., high-density polyethylene (HDPE) container to another HDPE container).
3. Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon).
4. A change in or addition of a cap liner.
5. A change in an antioxidant, colorant, stabilizer, anti-static agent, or mold-releasing agent for production of the container and/or closure to one that is used at similar levels in the packaging of a drug substance that was submitted to the Program for verification and that received approval to use the Certification mark.

**Labeling:**

1. Changes in the layout of the package or container label that are consistent with local, state, federal/national, or other applicable laws, regulations, or other applicable requirements without a change in the content of the labeling.
2. Editorial changes such as adding a distributor's name.
3. Labeling changes made to comply with an official compendium.
4. Addition of a foreign language text other than English provided the translation has been approved by a qualified foreign language expert or institution such as an embassy or a consul general's office.

**Miscellaneous changes:**

Tightening of acceptance criteria to provide greater assurance of drug substance purity.

Upon receipt of information regarding such changes, USP will review and determine whether the changes are deemed to be major, moderate, or minor. The criteria for such a determination will be made available, in writing, to the participant. If necessary, USP may require the drug substance or participant to be re-evaluated or the drug substance retested. If re-evaluation is not required, the participant may continue to use the USP verification status in accordance with licensed terms.

If re-evaluation is required, USP will immediately notify the participant in writing. USP also may require the participant to cease continued use of the USP verification status until the re-evaluation has been completed.

The participant may appeal the decision to require re-evaluation or retesting under the procedures described in Section 18 "APPEALS"; however, the participant shall not have the right to appeal the decision requiring them to cease using the USP verification status until the final decision is made regarding the status of re-evaluation or retesting.

## 16. PARTICIPANT'S INTERNAL AUDITS, USP AUDITS, AND ANNUAL REPORTS

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Results reported from the participant's internal audits will be used to monitor the state of operations within the participant's site(s) in between audits conducted by USP.

An on-site audit will be conducted by USP at the time of initial enrollment in the Program and at the three-year renewal point. More frequent audits by USP may be conducted on a for-cause basis, in response to a major change, or as a follow up to the initial audit when Action Level 1 deficiencies were noted, see section 13 USP DRUG SUBSTANCE VP REPORT OF FINDINGS. When the participant conducts an internal audit, the criteria listed in section 12 ON-SITE AUDIT CRITERIA should be consulted.

The participant must report the following annually to USP, with the first report due thirteen (13) months after the initial audit:

- Lot numbers and dates of manufacture of all batches of verified drug substances manufactured during the preceding year.
- Any deviations recorded in these drug substances.
- Audit findings from any internal audit(s) conducted using the On-site Audit Checklist guide.
- List of major, moderate, and minor changes.

If any compliance issues arise during the review of the annual report, USP reserves the right to conduct additional on-site audits.

Companies with multi-national sites will be allowed to submit their corporate audit report for the sites manufacturing the verified drug substance.

## 17. POST-VERIFICATION SURVEILLANCE

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After the Certification Mark is awarded to a drug substance, USP will perform, at a minimum, an annual evaluation of the drug substance to ensure that it continues to meet the Program criteria. Participants will be required to submit samples from their manufacturing site(s) to support this surveillance.

USP will contact the participant and request a list of the lots bearing the Certification Mark that are available for post-verification testing (requesting lot numbers and manufacturing dates). From that list, USP will randomly select a minimum of one lot for each drug substance to perform post-verification testing. USP will request samples of the lot(s) from the participant. Alternatively, Program staff may collect samples of the lot(s) from the participant. The samples received by USP will be tested in accordance with the compendial or participant's specification. Subsequently, USP will request, at a minimum, the release specification and analytical procedures used by the participant. USP also may request further documentation based on the drug substance that was verified. USP may in its sole discretion perform testing beyond the testing specified by the participant and will likely do so if there is a reasonable probability that the substance contains known contaminants or degradation products.

## 18. APPEALS

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In certain situations USP may refuse to issue, suspend, or revoke the use of the Certification Mark to participants. Participants may appeal the following:

- Rejection of pre-audit, quality control, or manufacturing documentation; test results; surveillance results; or audit reports.
- Recommendations for product recalls.
- Suspension or revocation of the Certification Mark.
- An initial decision not to award the Certification Mark is final. It may not be appealed.

### **Rejection based on deficiencies in documentation, test results, or audit reports**

Among other things, USP may reject as insufficient:

- Documentation that fails to meet the requirements for pre-audit, quality control, or manufacturing documentation.
- Test results that fail to demonstrate that the drug substance meets the labeled amount or other acceptance criteria (for initial verification and post-verification surveillance).
- Audit reports that show deficiencies or deviations from good manufacturing practices at the facility.

USP will send written notification of rejection to the participant, along with any relevant findings or reports. The participant will have the opportunity to appeal the rejection or take corrective action(s). Subsequently, if USP rejects the corrective action(s), the participant may appeal that rejection. The participant must send a written notice of appeal, along with any supporting evidence, within 40 calendar days from the date of receiving the written notification from USP.

USP's Appeals Panel will review the evidence received with the appeal and decide to accept or reject the participant's data and/or audit reports. In either case, written notification of the decision will be sent to the participant within 30 calendar days after receipt of participant's appeal. If the data and/or audit reports are accepted, USP will resume evaluation of the participant and data at the appropriate step in the Program process. If the data and/or reports are rejected, the participant can re-enter the program after correcting the deficiencies.

### **Product recalls**

USP may recommend a product recall if critical drug substance deficiencies are detected. Drug substance deficiencies are considered critical if:

- There is even a remote probability that the use of, or exposure to, the drug substance may cause serious adverse health consequences or death when used as intended.

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- There is even a reasonable probability that the use of, or exposure to, the drug substance may cause temporary or medically reversible adverse health consequences when used as intended.
- An official from the participant has submitted fraudulent documents to the USP.
- An official organization, such as FDA, has recommended voluntary recall.

Upon recommending a recall, USP will immediately notify the participant. Within 24 hours of such a recall recommendation, USP will convene a hearing – by conference call – with the participant's representative(s), who must answer any questions and provide the requested information about the drug substance problem. USP will then affirm or reverse its recommendation to recall the drug substance. If USP decides that a recall is to be recommended, it will immediately contact the appropriate governmental agency, such as FDA in the USA, and notify the participant to discontinue the use of the Certification Mark on the drug substance. The participant must take immediate action to do so but may appeal, within seven (7) calendar days, the decision to discontinue the use of the mark. The Program License Agreement requires participants to release and hold USP harmless for any reports that it files in good faith with appropriate governmental authorities and for any decisions it makes regarding participants' applications for continued maintenance of verification under the Program.

### **Suspension of the USP verification**

The following examples are illustrative and do not represent an exhaustive list. USP may suspend a participant's right to use the Certification Mark due to:

- Violation of any Program participation criteria, policies, or procedures by the participant, its affiliates, or agents.
- Major drug substance deficiencies, which include a major deviation from drug substance standards and/or manufacturing process.
- Major changes to a drug substance's specification, process control data, raw material source, equipment, manufacturing site change, testing, or any other change deemed essential by the participant, which must immediately be reported in writing to USP. USP will review the information and determine whether or not to suspend use of the Certification Mark during re-evaluation or retesting of the drug substance. Such work may include review of analytical data or additional audits at the participant's expense.

The participant may appeal USP's decision to suspend use of the Certification Mark. The appeal, along with any supporting evidence, must be made within 30 calendar days from the receipt of notification of suspension from USP. If no appeal is made within this period, the suspension becomes a revocation of the use of the Certification Mark and withdrawal of verification status with no further rights of appeal.



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When submitting the appeal, the participant may request a review of analytical procedures data, documentation, or an audit. USP will conduct such review or audit at the participant's expense and provide a written report of findings to the participant.

The participant may, on appeal, also request an oral hearing. USP will set a place, time, and date—not more than 60 calendar days after receiving the hearing request—and notify the participant. USP and the participant may present evidence at the hearing to a USP Appeals Panel. The participant may be represented by counsel. The Chair of the Appeals Panel will preside over and determine any other procedures that will govern the hearing. The participant shall pay all reasonable expenses incurred by USP including, but not limited to, travel expenses.

The USP Appeals Panel will issue a written determination with supporting reasons within 30 calendar days, if in the hearing it is found that the participant:

- Is substantially out of compliance with the Program criteria—in which case USP will revoke participant's verification status and use of the Certification Mark.
- Is substantially in compliance with the Program criteria—in which case USP will reverse the suspension and reinstate use of the mark.
- Can conduct corrective action within six months to become substantially compliant with Program criteria—in which case USP will affirm the suspension until further review. The participant must notify USP within 25 calendar days that it will seek the review. The participant will bear the cost of such review by USP. The participant's failure to notify USP within 25 calendar days, or to be in substantial compliance within six months, will result in revocation of verification status and use of the Certification Mark.

The decision of the USP Appeals Panel is final. In accordance with the Program License Agreement, participants must agree not to file a legal action challenging any such decision by USP or the USP Appeals Panel. Upon revocation of use of the Certification Mark, a participant may re-enter the program one year from such revocation, on payment of full fees.

**19. GLOSSARY**

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**802 Country:** A country that is recognized under section 802(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act and to which a drug or device may be exported, without having the drug or device approved by the U.S. Food and Drug Administration, if the drug or device complies with the laws of that country and has valid marketing authorization by the appropriate authority. These countries include Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and countries within the European Union or European Economic Area (the European Union and the European Free Trade Association) if the drug or device is marketed in that country or is authorized for general marketing in the European Economic Area.

**Acceptance Criteria:** predetermined limits (e.g., number, numerical range) against which sample data are compared to determine compliance with standards of quality.

**Adequate:** item/area/system/knowledge that meets basic minimum requirements.

**AG:** Advisory Group - a group of representatives from drug substance manufacturing companies and users of drug substances that provide advice for the manuals and requirements of the Program. The members are selected by USP on an annual basis.

**Appeals Panel:** a group consisting of two (2) members from appropriate USP Expert Committees; the USP Director of Quality Assurance; and additional USP staff. The Panel will have the authority to review appeals submitted by companies participating in the Program regarding: (1) rejection of data, process controls, or audit reports; (2) product recalls; or (3) suspension of the use of the mark.

**Auditor:** any Program staff member or USP approved audit firm/consultant that performs the on-site audit.

**Batch (or Lot):** a specific quantity of a drug substance or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

**Commercial Scale:** the manufacturing of a drug substance on production manufacturing scale for commercial use.

**Concomitant Component:** a substance found in a drug substance that is not the intended chemical entity, but that may be necessary for assuring the proper performance of the drug substance in its intended use, and is not an impurity or a foreign substance.

**Council of Experts (CoE):** The elected chairs of Expert Committees.

**Critical/Key Intermediate:** An intermediate in which an essential molecular characteristic(s), usually involving the proper stereochemical configuration required for structure/activity (pharmacological and/or physiological activity of the API) is first introduced into the structure (e.g., introduction of a chiral center)

**Current Quality System:** the quality control system and manufacturing process in place since the last instituted change to the drug substance manufacturing operation.

**Drug Substance Deficiencies (Action Level 1):** include the following: (1) a reasonable probability that the use of, or exposure to, the drug substance may cause serious adverse health consequences or death when used as intended; (2) a remote probability that the use of, or exposure to, the drug substance may cause temporary or medically reversible adverse health consequences when used as intended; (3) a participant's representative has submitted fraudulent documents to the Program; or (4) an official organization, such as the FDA, has recommended a voluntary recall.

**Drug Substance Deficiencies (Action Level 2):** include the following: (1) deviations from drug substance standards that would render the drug substance unusable for its intended purpose; (2) a lack of essential drug substance criteria that would render the drug substance unusable for its intended purpose; or (3) the participants, affiliates, or agents engage in violation of any Program participation criteria, policy, or procedure.

**Drug Substance Deficiencies (Action Level 3):** deviations from drug substance standards that show evidence of minor manufacturing and/or quality control problems.

**EC:** USP Expert Committee. One of USP's scientific standard-setting bodies

*EP:* *European Pharmacopoeia.*

**EPA:** U.S. Environmental Protection Agency.

**FDA:** U.S. Food and Drug Administration.

**Federal FD and C Act:** the Federal Food, Drug, and Cosmetic Act.

**Foreign Substance:** a component present in the drug substance, but not introduced into the drug substance as a consequence of its synthesis or purification and is not necessary to achieve the proper performance of the drug substance

**Good Manufacturing Practices:** the requirements found in the legislation, regulations, and administrative provisions for methods to be used in, and the facilities or controls to be used for, the manufacturing, processing, packing, and/or holding of a drug to assure that such drug meets the requirements as to safety, and has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to process. GMPs are that part of

## UNITED STATES PHARMACOPEIA Drug Substance Verification Program

quality assurance which ensures that products are consistently produced and controlled to quality standards.

**Impurity:** any component of the drug substance that is not the entity defined as the active ingredient or a concomitant component, but is present as a consequence of either the raw materials used or the manufacturing process and is not a foreign substance.

**Impurity Profile:** a description of the identified and unidentified impurities, and their acceptance criteria, present in a drug substance.

**Intermediate:** a material produced during steps of the manufacturing process of a drug substance that undergoes further chemical or physical change before it becomes the final drug substance.

*JP: Japanese Pharmacopoeia*

**Manufacturing Documentation:** the manufacturing directions, master batch formula/ manufacturing guide, and executed batch records.

**PAM:** FDA's Pesticide Analytical Manual is a repository of the analytical procedures used in FDA laboratories to examine food for pesticide residues for regulatory purposes (40 CFR 180.101 (c)). The manual is organized according to the scope of the analytical procedures in a two-volume set, available in Adobe Acrobat (pdf) format on the FDA's Web site.

**Pilot Scale:** the manufacturing of a drug substance on a reduced scale by processes representative of and simulating those to be applied on a larger, production manufacturing scale.

**Procedure:** a detailed set of instructions (methodology) used to generate analytical data.

**QA:** Quality Assurance.

**QC:** Quality Control.

**Raw Material:** any ingredient or starting material intended for use in the manufacture of a drug substance, which is not intended to be present in the drug substance.

**Recall:** a participant's removal or correction of its marketed drug substance directed by the USP, an official organization such as the FDA, or the participant initiates due to a critical drug substance deficiency.

**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. They are not completely

removed by practical manufacturing techniques. (See *USP* General Chapter <467> *Residual Solvents*.)

**Retest Date:** the interval of time for which the drug substance must conform to applicable specifications when stored under labeled conditions. The retest date should be supported by stability data and be indicated on the drug substance label and exterior commercial packaging.

**Should:** used to state recommended or advisory procedures or to identify recommended equipment.

**Specification:** includes the tests, analytical test procedures, and acceptance criteria that define the standard of quality for a material.

**SOP:** Standard Operating Procedure.

**Stability Protocol:** documents describing the sample, test specifications, test intervals, conditions, and packaging used to determine the shelf-life.

**USP-NF:** the current official volume of the *United States Pharmacopeia-National Formulary* including its supplements.

**USP Reference Standard:** substances selected for their high purity, critical characteristics, and suitability for the intended purpose. They are used to test for compliance with *USP-NF* requirements, in order to demonstrate identification, strength, quality, and purity of official articles.

## 20. FORMS AND CHECKLISTS

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- Pre-Audit Documentation Checklist
- Chemistry and Manufacturing Controls (CMC) Documentation Checklist
- On-Site Audit Checklist

UNITED STATES PHARMACOPEIA Drug Substance Verification Program

<b>Pre-Audit Documentation Checklist for Drug Substance/Dietary Ingredient/Excipient</b>				
<b>Participant Information</b>				
Name of Company/Site			Year Site Established	
Address		No. of Sites:	Size of Facility	
Name and Title of Primary Contact		Phone Number	Fax	Email
Name and Title of Secondary Contact		Phone Number	Fax	Email
<b>Employees</b>				
Total Number	Manufacturing	QC	QA	Other
<b>Ingredients</b>				
List all Ingredients manufactured at site and indicate which ingredients are to be submitted for verification. (Attach additional sheets if necessary.)				
<b>Pre-Audit Documentation</b> Complete documentation, in the requested format, needs to be received before the review may begin.				
Please include standard operating procedures or descriptions of the following in the pre-audit documentation package			<b>Shaded area to be completed by USP VER Staff</b> (If "NAC" or "MI" Box is checked, VER observation(s) will be provided to Participant.  AC = Acceptable      NAC = Not Acceptable MI = Missing Information    N/A = Not Applicable	
Section: Subject				
<b>1. Flow Diagram(s) of Manufacturing Process:</b> <i>Flow Diagram(s) of Manufacturing Process(es) Showing Material Inputs and Outputs, and Key Intermediates</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
<b>2. Quality Management:</b> <i>Responsibilities of the Quality Unit(s), Responsibility for Production Activities, Internal Audits(Self Inspection), and Product Quality Reviews</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
<b>3. Personnel:</b> <i>Organizational Chart Including All Key Manufacturing Laboratory, QA and QC Personnel, Personnel Qualifications, Consultants, and Training Programs</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
<b>4. Building and Facilities Site/Building Map:</b> <i>Design and Construction, Utilities, Water, Containment, Lighting, Sewage and Refuse, Sanitation and Maintenance</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
<b>5. Process Equipment:</b> <i>Design and Construction, Equipment Maintenance, and Cleaning Procedures, Calibration, and Computerized systems</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
<b>6. Documentation and Records:</b> <i>Documentation Systems and Specifications, Equipment Cleaning and Use Record, Records of Raw Materials, Intermediates, Ingredient Labeling and Packaging Materials, Master Production Instructions (Master Production and Control Records), Batch Production Records (Batch Production and Control Records), Laboratory Control Records, and Batch Production Record Review</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
<b>7. Materials Management:</b> <i>General Controls, Receipt and Quarantine, Sampling and Testing of Incoming Production Materials, Storage, Re-Evaluation</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
<b>8. Production and In-Process Controls:</b> <i>Production Operations, Time limits, In-process Sampling and Controls, Blending Batches of Intermediates or Ingredients, Contamination Control</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
<b>9. Packaging and Identification Labeling of Ingredients and Intermediates:</b> <i>General Controls, Packaging Materials, Label Issuance and Control, Packaging and Labeling Operations</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
<b>10. Storage and Distribution:</b> <i>Warehouse Procedures, Distribution Procedures</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
<b>11. Laboratory Controls:</b> <i>General Controls, Testing of Intermediates and Ingredients, Certificates of Analysis, Stability Monitoring of Ingredients, Expiry and Retest Dating, Reserve/Retention Samples, Validation of Analytical Procedures (also see Validation Section)</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC

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<b>12. Validation:</b> <i>Validation Policy, Validation Documentation, Equipment Qualification, Process Validation Program, Periodic Review of Validated Systems, Cleaning Validation, Validation of Analytical Methods</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>13. Change Control:</b> <i>Formal Change Control System, Identification, Documentation, Review, and Approval of Changes in Raw Materials, Specifications, Analytical Methods, Facilities, Support Systems, Equipment, Computers, Processing Steps, Labeling and Packaging Materials</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>14. Rejection and Re-Use of Materials:</b> <i>Rejection, Reprocessing, Reworking, Recovery of Materials and Solvents and Returns</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>15. Complaints and Recalls:</b> <i>Procedures for Quality Related Complaints, Recall Procedure</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>16. Contract Manufacturers and Laboratories:</b> <i>Contract Approval, Evaluation Process</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>17. Agents, Brokers, Traders, Distributors, Repackers, and Relabelers:</b> <i>Quality Management Traceability of Distributed Ingredients and Intermediates, Repackaging, Relabeling and Holding of Ingredients and Intermediates, Stability, Complaints and Recalls</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>18. Specific Guidance for Ingredients Manufactured by Cell Cultures or Fermentation:</b> <i>Cell Bank Maintenance and Record Keeping, Cell Culture/Fermentation, Harvesting, Isolation and Purification, Viral Removal/Inactivation Steps.</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
Comments and Attachments:				
Reported By: _____ Printed Name	_____ Signature	Date: _____		
Reviewed By: _____ Printed Name	_____ Signature	Date: _____		



## II. Chemistry and Manufacturing Controls (CMC) Documentation Checklist for Drug Substances, Dietary Ingredients, or Excipients

<b>II. Chemistry and Manufacturing Controls (CMC) Documentation Checklist for Drug Substances, Dietary Ingredients, or Excipients</b>			
<b>PARTICIPANT INFORMATION</b>			
COMPANY NAME			
ADDRESS			
NAME AND TITLE OF PRIMARY CONTACT			PHONE NUMBER
NAME AND TITLE OF SECONDARY CONTACT			PHONE NUMBER
INGREDIENT NAME	INGREDIENT TYPE <input type="checkbox"/> DRUG SUBSTANCE <input type="checkbox"/> DIETARY INGREDIENT <input type="checkbox"/> EXCIPIENT	INGREDIENT ITEM CODE	CMC DOCUMENTATION USP VER REFERENCE NUMBER
<b>Ingredient Information</b>			
Complete documentation, in the requested format, needs to be received before review begins.			
<i>Note: In some instances (e.g. more than one drug substance, manufacturing site, manufacturing process, etc.) information may be repeated or presented separately in multiple sections, in which case, it should be made clear what the section refers to by creating distinguishing title in parentheses (Name, manufacturer) following the section header. Cross references to information in other sections is acceptable. ICH guidelines that apply to a given section are referenced at the end of the section, in parentheses.</i>			SHADED AREA TO BE COMPLETED BY USP VER Staff (If "NAC" or "MI" Box is checked, USP VER observation will be provided on the VER observation form and coded under Section ID as "II 1.1, II 1.2, etc." to assign appropriate observation to Form and Section.)
<b>Contents of the Ingredient Information to be provided</b>			AC = Acceptable NAC = Not Acceptable MI = Missing Information N/A = Not Applicable
<b>1.0 General Information:</b>			
<b>1.1 Nomenclature:</b> <i>International Nonproprietary Name, Compendial name, Chemical name, Company or laboratory code, Chemical Abstracts Service registry number, other non-proprietary name(s)</i>			<input type="checkbox"/> AC <input type="checkbox"/> NAC <input type="checkbox"/> MI <input type="checkbox"/> N/A
<b>1.2 Structure:</b> <i>The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass</i>			<input type="checkbox"/> AC <input type="checkbox"/> NAC <input type="checkbox"/> MI <input type="checkbox"/> N/A
<b>1.3 General Properties:</b> <i>A list of physicochemical and other relevant properties of the drug substance. (ICH Q6A)</i>			<input type="checkbox"/> AC <input type="checkbox"/> NAC <input type="checkbox"/> MI <input type="checkbox"/> N/A
<b>2.0 Manufacture:</b>			
<b>2.1 Manufacturer(s):</b> <i>The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing</i>			<input type="checkbox"/> AC <input type="checkbox"/> NAC <input type="checkbox"/> MI <input type="checkbox"/> N/A
<b>2.2 Description of Manufacturing Process and Process Controls:</b> <i>A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical</i>			<input type="checkbox"/> AC <input type="checkbox"/> NAC <input type="checkbox"/> MI <input type="checkbox"/> N/A

## II. Chemistry and Manufacturing Controls (CMC) Documentation Checklist for Drug Substances, Dietary Ingredients, or Excipients

<p><i>structures of starting materials, intermediates, reagents and ingredient reflecting stereochemistry, and identifies operating conditions and solvents.</i></p> <p><i>A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time).</i></p>				
<p><b>2.2.1 Biotech:</b> <i>For biotech, information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions (ICH Q5A, Q5B, and Q6B).</i></p>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<p><b>2.2.2 Alternate Processes:</b> <i>Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or provided as part of the file (in Section 2.5).</i></p>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<p><b>2.3 Control of Materials:</b> <i>Materials used in the manufacture of the ingredient (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization (ICH Q6A and Q6B).</i></p>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<p><b>2.4 Controls of Critical Steps and Intermediates:</b> <i>Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in the manufacturing process to ensure that the process is controlled should be provided. For Intermediates, information on the quality and control of intermediates isolated during the process should be provided (ICH Q6A and Q6B).</i></p>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<p><b>2.5 Process Validation and/or Evaluation:</b> <i>Process validation and/or evaluation studies for aseptic processing and sterilization should be included.</i></p>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<p><b>2.6 Manufacturing Process Development:</b> <i>The developmental history of the manufacturing process, as described in Section 2.2, should be provided. A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site or critical equipment of the ingredient used in producing nonclinical, clinical, scale-up, pilot, and/or production scale batches. The reason for the changes should be explained. The significance of each change should be assessed by evaluating its potential to impact the quality of the ingredient and/or intermediate, if appropriate (ICH Q3A).</i></p>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>3.0 Characterization:</b>				
<p><b>3.1 Elucidation of Structure and other Characteristics:</b> <i>Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included (ICH Q6A).</i></p>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<p><b>3.2 Impurities:</b> <i>Information on impurities should be provided (ICH Q3A, Q3C, and Q6A).</i></p>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>4.0 Control of Ingredient:</b>				
<p><b>4.1 Specifications:</b> <i>The specifications for the ingredient should be provided (ICH Q6A).</i></p>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<p><b>4.2 Analytical Procedures:</b> <i>The analytical procedures used for testing the ingredient should be provided (ICH Q6A).</i></p>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A

<b>II. Chemistry and Manufacturing Controls (CMC) Documentation Checklist for Drug Substances, Dietary Ingredients, or Excipients</b>				
<b>4.3 Validation of Analytical Procedures:</b> <i>The analytical validation information, including experimental data for the analytical procedures used for testing the ingredient should be provided (ICH Q2A and Q2B).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>4.4 Batch Analyses:</b> <i>A copy of master batch records and executed batch records for batches selected by USP should be provided. Description of selected batches and results of batch analyses should be provided (ICH Q3A, Q3C and Q6A).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>4.5 Justification of Specification:</b> <i>Justification for the ingredient specification should be provided (ICH Q3A, Q3C and Q6A).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>5.0 Reference Standards or Materials:</b> <i>Information on the reference standards or reference materials used for testing of the ingredient should be provided (ICH Q6A).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>6.0 Container Closure System:</b> <i>A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.</i>  <i>For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.</i>  <i>The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the pharmaceutical ingredient, including sorption to container and leaching, and/or safety of materials of construction.</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>7.0 Stability:</b>				
<b>7.1 Stability Summary and Conclusions:</b> <i>The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate (ICH Q1A and Q1B).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>7.2 Post-approval Stability Protocol and Stability Commitment:</b> <i>The post-approval stability protocol and stability commitment should be provided (ICH Q1A).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>7.3 Stability Data:</b> <i>Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included (ICH Q1A, Q1B, Q2A, and Q2B).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>8.0 Facilities and Equipment:</b> <i>A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) 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 product.</i> <i>Information on all developmental or commercial products manufactured or manipulated in the same areas as the applicant's product should be included.</i> <i>A summary description of 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.</i> <i>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</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A

**II. Chemistry and Manufacturing Controls (CMC) Documentation  
Checklist for Drug Substances, Dietary Ingredients, or Excipients**

<i>areas and equipment.</i>				
<b>9.0 Adventitious Agents Safety Evaluation:</b> <i>Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section. Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent (ICH Q5A, Q5D, and Q6B).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>10.0 Excipients:</b> <i>If appropriate for an ingredient containing additives, where novel or noncompendial nonnovel excipients is proposed and a significant amount of data is provided for the excipient, this information should be provided in this section and should follow the same format and level of subsections as for the ingredient.</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
<b>11.0 Regional Information:</b> <i>The information in this section should be consistent with the requirements of the relevant region.</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
Comments and Attachments:				
Reported By: _____ Date: _____ Printed Name Signature				
Reviewed By: _____ Date: _____ Printed Name Signature				

UNITED STATES PHARMACOPEIA Drug Substance Verification Program

On-Site Audit Checklist for Drug Substance (DS) or Dietary Ingredient (DI)

COMPANY NAME: \_ \_\_\_\_\_

DATE(S) OF AUDIT: \_ \_\_\_\_\_

LOCATION [ADDRESS]: \_\_\_\_\_

ESCORTS [NAME(S) AND TITLE(S)]: \_ \_\_\_\_\_

AUDITOR(S) [NAME(S) AND TITLE(S)]: \_ \_\_\_\_\_

**NOTE:** THIS CHECKLIST IS DESIGNED AS AN AID OR TOOL TO BE USED BY EXPERIENCED AUDITORS IN CONDUCTING AUDITS. IT IS NOT NECESSARILY INTENDED TO BE ALL-INCLUSIVE OR TO LIMIT THE SCOPE OF THE AUDIT. IDEALLY, ONE LOT OF DRUG SUBSTANCE/DIETARY INGREDIENT (DS/DI) SHOULD BE TRACKED FROM THE START OF PRODUCTION TO RELEASE OF THE FINAL INGREDIENT.

INDEX FOR CHECKLIST:

1. INTRODUCTION
2. QUALITY MANAGEMENT
3. PERSONNEL
4. BUILDINGS AND FACILITIES
5. PROCESS EQUIPMENT
6. DOCUMENTATION AND RECORDS
7. MATERIALS MANAGEMENT
8. PRODUCTION AND IN-PROCESS CONTROLS
9. PACKAGING AND IDENTIFICATION LABELLING OF DS/DIs AND INTERMEDIATES
10. STORAGE AND DISTRIBUTION
11. LABORATORY CONTROLS
12. VALIDATION
13. CHANGE CONTROL
14. REJECTION AND REUSE OF MATERIALS
15. COMPLAINTS AND RECALLS
16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)
17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (-/ = YES)
<b>ON-SITE AUDIT CHECKLIST</b>					
<b>1. INTRODUCTION</b>					
1.1 DS/DIs are manufacture by (√ all that apply): <input type="checkbox"/> Chemical synthesis <input type="checkbox"/> Extraction <input type="checkbox"/> Cell culture/fermentation <input type="checkbox"/> Recovery from natural sources					
1.2 Company should designate and document the rationale for the point at which production of the DS/DI begins.					
1.3 Brief company history					
1.4 Status of last FDA or other regulatory inspection					
1.5 Other sites/companies involved in operations					
<b>2. QUALITY MANAGEMENT</b>					
<b>2.1 Principles</b>					
2.10 Quality should be the responsibility of all persons involved in manufacturing.					
2.11 Each manufacturer should establish, document, and implement an effective system for managing quality					
2.12 The system for managing quality should encompass the organizational structure, procedures, processes and resources, and manufacturing activities. All quality related activities should be defined and documented.					
2.13 There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities.					
2.14 The persons authorized to release intermediates and DS/DIs should be specified.					
2.15 All quality related activities should be recorded at the time they are performed.					
2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.					
2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use.					
2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g., quality related complaints, recalls, regulatory actions, etc.).					
<b>2.2 Responsibilities of the Quality Unit(s)</b>					
2.20 The quality unit(s) should be involved in all quality-related matters.					
2.21 The quality unit(s) should review and approve all appropriate quality-related documents.					
2.22 The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to:					
2.22.1 Releasing or rejecting all DS/DIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company.					
2.22.2 Establishing a system to release or reject raw materials, intermediates, packaging and labeling materials					
2.22.3 Reviewing completed batch production and laboratory control records of critical process steps before release of the DS/DI for distribution					
2.22.4 Making sure that critical deviations are investigated and resolved					

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GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (-/= YES)
2.22.5 Approving all specifications and master production instructions					
2.22.6 Approving all procedures impacting the quality of intermediates or DS/DIs					
2.22.7 Making sure that internal audits (self-inspections) are performed					
2.22.8 Approving intermediate and DS/DI contract manufacturers					
2.22.9 Approving changes that potentially impact intermediate or DS/DI quality					
2.22.10 Reviewing and approving validation protocols and reports					
2.22.11 Making sure that quality related complaints are investigated and resolved					
2.22.12 Making sure that effective systems are used for maintaining and calibrating critical equipment					
2.22.13 Making sure that materials are appropriately tested and the results are reported					
2.22.14 Making sure that there is stability data to support retest or expiry dates and storage conditions on DS/DIs and/or intermediates where appropriate					
2.22.15 Performing product quality reviews (as defined in Section 2.5)					
<b>2.3 Responsibility for Production Activities</b>					
2.3.1 Preparing, reviewing, approving and distributing the instructions for the production of intermediates or DS/DIs according to written procedures					
2.3.2 Producing DS/DIs and, when appropriate, intermediates according to pre-approved instructions					
2.3.3 Reviewing all production batch records and ensuring that these are completed and signed					
2.3.4 Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded					
2.3.5 Making sure that production facilities are clean and when appropriate disinfected					
2.3.6 Making sure that the necessary calibrations are performed and records kept					
2.3.7 Making sure that the premises and equipment are maintained and records kept					
2.3.8 Making sure that validation protocols and reports are reviewed and approved					
2.3.9 Evaluating proposed changes in product, process or equipment					
2.3.10 Making sure that new and, when appropriate, modified facilities and equipment are qualified.					
<b>2.4 Internal Audits (Self Inspection)</b>					
2.40 In order to verify compliance with the principles of GMP for DS/DIs, regular internal audits should be performed in accordance with an approved schedule.					
2.41 Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.					
<b>2.5 Product Quality Review</b>					

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2.50	Regular quality reviews of DS/DIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:					
2.50.1	A review of critical in-process control and critical DS/DI test results					
2.50.2	A review of all batches that failed to meet established specification(s)					
2.50.3	A review of all critical deviations or non-conformances and related investigations					
2.50.4	A review of any changes carried out to the processes or analytical methods					
2.50.5	A review of results of the stability monitoring program					
2.50.6	A review of all quality-related returns, complaints and recalls					
2.50.7	A review of adequacy of corrective actions					
2.51	The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.					
<b>3. PERSONNEL</b>						
<b>3.1 Personnel Qualifications</b>						
3.10	There should be an adequate number of personnel qualified by appropriate education, training and/or experience.					
3.11	The responsibilities of all personnel should be specified in writing.					
3.12	Training should be regularly conducted by qualified individuals for GMP functions. Records of training should be maintained. Training should be periodically assessed.					
<b>3.2 Personnel Hygiene</b>						
3.20	Personnel should practice good sanitation and health habits.					
3.21	Personnel should wear clean clothing and additional protective apparel.					
3.22	Personnel should avoid direct contact with intermediates or DS/DIs.					
3.23	Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.					
3.24	Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of DS/DI.					
<b>3.3 Consultants</b>						
3.30	Consultants advising on the manufacture and control of intermediates or DS/DIs should have sufficient education, training, and/or experience.					
3.31	Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.					
<b>4. BUILDINGS AND FACILITIES</b>						
<b>4.1 Design and Construction</b>						
4.10	Buildings and facilities used in the manufacture of intermediates and DS/DIs should be located, designed, and constructed to facilitate cleaning, maintenance, operations, and minimize potential contamination.					
4.11	Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.					
4.12	Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.					



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4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.					
4.14 There should be defined areas or other control systems for the following activities:					
4.14.1 Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection					
4.14.2 Quarantine before release or rejection of intermediates and DS/DIs					
4.14.3 Sampling of intermediates and DS/DIs					
4.14.4 Holding rejected materials before further disposition (e.g., return, reprocessing or destruction)					
4.14.5 Storage of released materials					
4.14.6 Production operations					
4.14.7 Packaging and labeling operations					
4.14.8 Laboratory operations					
4.15 Adequate, clean washing and toilet facilities should be provided for personnel and should be separate from, but easily accessible to, manufacturing areas.					
4.16 Laboratory areas/operations should normally be separated from production areas.					
<b>4.2 Utilities</b>					
4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.					
4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where DS/DIs are exposed to the environment.					
4.22 If air is re-circulated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.					
4.23 Permanently installed pipe work should be appropriately identified and located to avoid risks of contamination of the intermediate or DS/DI.					
4.24 Drains should be of adequate size and should be provided with an air break.					
<b>4.3 Water</b>					
4.30 Water used in the manufacture of DS/DIs should be demonstrated to be suitable for its intended use.					
4.31 Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.					
4.32 If drinking (potable) water is insufficient to assure DS/DI quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.					
4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.					
4.34 Where the manufacturer of a non-sterile DS/DI either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.					
<b>4.4. Containment</b>					
4.40 Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.					

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4.41	Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.					
4.42	Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another.					
4.43	Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of DS/DIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from DS/DIs.					
<b>4.5 Lighting</b>						
4.50	Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.					
<b>4.6 Sewage and Refuse</b>						
4.60	Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.					
<b>4.7 Sanitation and Maintenance</b>						
4.70	Buildings used in the manufacture of intermediates and DS/DIs should be properly maintained and repaired and kept in a clean condition.					
4.71	Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.					
4.72	When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and DS/DIs.					
<b>5. PROCESS EQUIPMENT</b>						
<b>5.1 Design and Construction</b>						
5.10	Equipment used in the manufacture of intermediates and DS/DIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.					
5.11	Equipment should be constructed so that surfaces that contact raw materials, intermediates, or DS/DIs do not alter the quality of the intermediates DS/DIs beyond the official or other established specifications.					
5.12	Production equipment should only be used within its qualified operating range.					
5.13	Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or DS/DI should be appropriately identified.					
5.14	Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or DS/DIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.					
5.15	Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.					
5.16	A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).					

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<b>ON-SITE AUDIT CHECKLIST</b>					
<b>5.2 Equipment Maintenance and Cleaning</b>					
5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.					
5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and DS/DIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:					
5.21.1 Assignment of responsibility for cleaning of equipment					
5.21.2 Cleaning schedules, including, where appropriate, sanitizing schedules					
5.21.3 A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment					
5.21.3 When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning					
5.21.4 Instructions for the removal or obliteration of previous batch identification					
5.21.5 Instructions for the protection of clean equipment from contamination prior to use					
5.21.6 Inspection of equipment for cleanliness immediately before use, if practical					
5.21.7 Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.					
5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or DS/DI beyond the official or other established specifications.					
5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).					
5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.					
5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.					
5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.					
<b>5.3 Calibration</b>					
5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or DS/DIs should be calibrated according to written procedures and an established schedule.					
5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.					
5.32 Records of these calibrations should be maintained.					
5.33 The current calibration status of critical equipment should be known and verifiable.					
5.34 Instruments that do not meet calibration criteria should not be used.					
5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or DS/DI(s) manufactured using this equipment since the last successful calibration.					
<b>5.4 Computerized Systems</b>					
5.40 GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.					
5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.					
5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.					
5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.					

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5.44 Written procedures should be available for the operation and maintenance of computerized systems.					
5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.					
5.46 Incidents related to computerized systems that could affect the quality of intermediates or DS/DIs or the reliability of records or test results should be recorded and investigated.					
5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.					
5.48 If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.					
5.49 Data can be recorded by a second means in addition to the computer system.					
<b>6. DOCUMENTATION AND RECORDS</b>					
<b>6.1 Documentation System and Specifications</b>					
6.10 All documents related to the manufacture of intermediates or DS/DIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.					
6.11 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.					
6.12 A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.					
6.13 All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For DS/DIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.					
6.14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.					
6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.					
6.16 Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.					
6.17 Specifications should be established and documented for raw materials, intermediates where necessary, DS/DIs, and labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or DS/DIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.					
6.18 If electronic signatures are used on documents, they should be authenticated and secure.					
<b>6.2 Equipment Cleaning and Use Record</b>					
6.20 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.					
6.21 If equipment is dedicated to manufacturing one intermediate or DS/DI, then individual equipment records are not necessary if batches of the intermediate or DS/DI follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.					
<b>6.3 Records of Raw Materials, Intermediates, DS/DI Labeling and Packaging Materials</b>					

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6.30 Records should be maintained including:					
6.30.1 The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labeling and packaging materials for DS/DI's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt					
6.30.2 The results of any test or examination performed and the conclusions derived from this					
6.30.3 Records tracing the use of materials					
6.30.4 Documentation of the examination and review of DS/DI labeling and packaging materials for conformity with established specifications					
6.30.5 The final decision regarding rejected raw materials, intermediates or DS/DI labeling and packaging materials.					
6.31 Master (approved) labels should be maintained for comparison to issued labels.					
<b>6.4 Master Production Instructions (Master Production and Control Records)</b>					
6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and DS/DI should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).					
6.41 Master production instructions should include:					
6.41.1 The name of the intermediate or DS/DI being manufactured and an identifying document reference code, if applicable					
6.41.2 A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics					
6.41.3 An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified					
6.41.4 The production location and major production equipment to be used					
6.41.5 Detailed production instructions, including the:					
6.41.5.1 Sequences to be followed					
6.41.5.2 Ranges of process parameters to be used					
6.41.5.3 Sampling instructions and in-process controls with their acceptance criteria, where appropriate					
6.41.5.4 Time limits for completion of individual processing steps and/or the total process, where appropriate					
6.41.5.5 Expected yield ranges at appropriate phases of processing or time					
6.41.6 Where appropriate, special notations and precautions to be followed, or cross-references to these					
6.41.7 The instructions for storage of the intermediate or DS/DI to assure its suitability for use, including the labeling and packaging materials and special storage conditions with time limits, where appropriate.					
<b>6.5 Batch Production Records (Batch Production and Control Records)</b>					
6.50 Batch production records should be prepared for each intermediate and DS/DI and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.					
6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.					
6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include:					

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6.52.1 Dates and, when appropriate, times					
6.52.2 Identity of major equipment (e.g., reactors, driers, mills, etc.) used					
6.52.3 Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing					
6.52.4 Actual results recorded for critical process parameters					
6.52.5 Any sampling performed					
6.52.6 Signatures of the persons performing and directly supervising or checking each critical step in the operation					
6.52.7 In-process and laboratory test results					
6.52.8 Actual yield at appropriate phases or times					
6.52.9 Description of packaging and label for intermediate or DS/DI					
6.52.10 Representative label of DS/DI or intermediate if made commercially available					
6.52.11 Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately					
6.52.12 Results of release testing					
6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or DS/DI to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.					
<b>6.6 Laboratory Control Records</b>					
6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:					
6.60.1 A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing					
6.60.2 A statement of or reference to each test method used					
6.60.3 A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions					
6.60.4 A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested					
6.60.5 A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors					
6.60.6 A statement of the test results and how they compare with established acceptance criteria					
6.60.7 The signature of the person who performed each test and the date(s) the tests were performed					
6.60.8 The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards					
6.61 Complete records should also be maintained for					
6.61.1 Any modifications to an established analytical method					
6.61.2 Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices					
6.61.3 All stability testing performed on DS/DIs					
6.61.4 Out-of-specification (OOS) investigations					
<b>6.7 Batch Production Record Review</b>					
6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or DS/DI with established specifications before a batch is released or distributed.					
6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an DS/DI batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).					

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6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.					
6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.					
<b>7. MATERIALS MANAGEMENT</b>					
<b>7.1 General Controls</b>					
7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.					
7.11 Manufacturers of intermediates and/or DS/DIs should have a system for evaluating the suppliers of critical materials.					
7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).					
7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or DS/DI manufacturer.					
7.14 Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.					
<b>7.2 Receipt and Quarantine</b>					
7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.					
7.21 Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.					
7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:					
7.22.1 Certificate of cleaning					
7.22.2 Testing for trace impurities					
7.22.3 Audit of the supplier.					
7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.					
7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.					
<b>7.3 Sampling and Testing of Incoming Production Materials</b>					
7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.					
7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.					
7.32 Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.					
7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.					
7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.					

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7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.					
<b>7.4 Storage</b>					
7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.					
7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.					
7.42 Materials should be stored under conditions and for a period that have no adverse affect on their quality, and should normally be controlled so that the oldest stock is used first.					
7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.					
7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.					
<b>7.5 Re-evaluation</b>					
7.50 Materials should be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).					
<b>8. PRODUCTION AND IN-PROCESS CONTROLS</b>					
<b>8.1 Production Operations</b>					
8.10 Raw materials for intermediate and DS/DI manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.					
8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:					
8.11.1 Material name and/or item code					
8.11.2 Receiving or control number					
8.11.3 Weight or measure of material in the new container					
8.11.4 Re-evaluation or retest date if appropriate					
8.12 Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or DS/DI.					
8.13 Other critical activities should be witnessed or subjected to an equivalent control.					
8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.					
8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.					
8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.					
8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.					
<b>8.2 Time Limits</b>					
8.20 If time limits are specified in the master production instruction (see 6.41), these time limits should be met to ensure the quality of intermediates and DS/DIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.					
8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.					
<b>8.3 In-process Sampling and Controls</b>					



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8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and DS/DIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.					
8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or DS/DI being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).					
8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).					
8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.					
8.34 Written procedures should describe the sampling methods for in-process materials, intermediates, and DS/DIs. Sampling plans and procedures should be based on scientifically sound sampling practices.					
8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or DS/DIs. Procedures should be established to ensure the integrity of samples after collection.					
8.36 Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.					
<b>8.4 Blending Batches of Intermediates or DS/DIs</b>					
8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or DS/DI. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.					
8.41 Out-Of-Specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.					
8.42 Acceptable blending operations include but are not limited to:					
8.42.1 Blending of small batches to increase batch size					
8.42.2 Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or DS/DI to form a single batch.					
8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.					
8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.					
8.45 Where physical attributes of the DS/DI are critical (e.g., DS/DIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.					
8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.					
8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.					
<b>8.5 Contamination Control</b>					
8.50 Residual materials can be carried over into successive batches of the same intermediate or DS/DI if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established DS/DI impurity profile.					
8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or DS/DIs by other materials.					
8.52 Precautions to avoid contamination should be taken when DS/DIs are handled after purification.					

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<b>9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES</b>					
<b>9.1 General</b>					
9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labeling materials.					
9.11 Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.					
9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.					
<b>9.2 Packaging Materials</b>					
9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or DS/DI that may occur during transportation and recommended storage.					
9.21 Containers should be clean and, where indicated by the nature of the intermediate or DS/DI, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or DS/DI beyond the specified limits.					
9.22 If containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.					
<b>9.3 Label Issuance and Control</b>					
9.30 Access to the label storage areas should be limited to authorized personnel.					
9.31 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).					
9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.					
9.33 Obsolete and out-dated labels should be destroyed.					
9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.					
9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.					
9.36 A printed label representative of those used should be included in the batch production record.					
<b>9.4 Packaging and Labeling Operations</b>					
9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.					
9.41 Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or DS/DIs.					
9.42 Labels used on containers of intermediates or DS/DIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or DS/DI.					
9.43 If the intermediate or DS/DI is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or DS/DIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or DS/DIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.					
9.44 Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.					
9.45 Packaged and labeled intermediates or DS/DIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.					

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GMP ITEM	<b>ON-SITE AUDIT CHECKLIST</b>	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (-/= YES)
9.46	Intermediate or DS/DI containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.					
<b>10. STORAGE AND DISTRIBUTION</b>						
<b>10.1 Warehousing Procedures</b>						
10.10	Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.					
10.11	Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.					
<b>10.2 Distribution Procedures</b>						
10.20	DS/DIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). DS/DIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.					
10.21	DS/DIs and intermediates should be transported in a manner that does not adversely affect their quality.					
10.22	Special transport or storage conditions for an DS/DI or intermediate should be stated on the label.					
10.23	The manufacturer should ensure that the contract acceptor (contractor) for transportation of the DS/DI or intermediate knows and follows the appropriate transport and storage conditions.					
10.24	A system should be in place by which the distribution of each batch of intermediate and/or DS/DI can be readily determined to permit its recall.					
<b>11. LABORATORY CONTROLS</b>						
<b>11.1 General Controls</b>						
11.10	The independent quality unit(s) should have at its disposal adequate laboratory facilities.					
11.11	There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.					
11.12	All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, DS/DIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).					
11.13	Appropriate specifications should be established for DS/DIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the DS/DI has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the DS/DI has a specification for endotoxins, appropriate action limits should be established and met.					
11.14	Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.					
11.15	Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.					
11.16	Reagents and standard solutions should be prepared and labeled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.					

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11.17 Primary reference standards should be obtained as appropriate for the manufacture of DS/DIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.					
11.18 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.					
11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.					
<b>11.2 Testing of Intermediates and DS/DIs</b>					
11.20 For each batch of intermediate and DS/DI, appropriate laboratory tests should be conducted to determine conformance to specifications.					
11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each DS/DI. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the DS/DI. Impurity profiles are normally not necessary for DS/DIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B.					
11.22 The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the DS/DI resulting from modifications in raw materials, equipment operating parameters, or the production process.					
11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and DS/DI where microbial quality is specified.					
<b>11.3 Validation of Analytical Procedures - see Section 12.</b>					
<b>11.4 Certificates of Analysis</b>					
11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or DS/DI on request.					
11.41 Information on the name of the intermediate or DS/DI including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or DS/DIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or DS/DIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.					
11.42 The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).					
11.43 Certificates should be dated and signed by authorized personnel of the quality unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address and telephone number of the repacker/reprocessor and a reference to the name of the original manufacturer.					
11.44 If new Certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these Certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.					
<b>11.5 Stability Monitoring of DS/DIs</b>					
11.50 A documented, on-going testing program should be designed to monitor the stability characteristics of DS/DIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.					
11.51 The test procedures used in stability testing should be validated and be stability indicating.					
11.52 Stability samples should be stored in containers that simulate the market container. For example, if the DS/DI is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.					
11.53 Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the DS/DI is expected to remain stable for at least two years, fewer than three batches can be used.					

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11.54	Thereafter, at least one batch per year of DS/DI manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.					
11.55	For DS/DIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other DS/DIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months, and at three month intervals after that. When data exist that confirm that the stability of the DS/DI is not compromised, elimination of specific test intervals (e.g. 9 month testing) can be considered.					
11.56	Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.					
<b>11.6 Expiry and Retest Dating</b>						
11.60	When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).					
11.61	A DS/DI expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.					
11.62	Preliminary DS/DI expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the DS/DI represents the material to be made on a commercial scale.					
11.63	A representative sample should be taken for the purpose of performing a retest.					
<b>11.7 Reserve/Retention Samples</b>						
11.70	The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of DS/DI and not for future stability testing purposes.					
11.71	Appropriately identified reserve samples of each DS/DI batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is the longer. For DS/DIs with retest dates, similar reserve samples should be retained for three years after the batch is completely distributed by the manufacturer.					
11.72	The reserve sample should be stored in the same packaging system in which the DS/DI is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.					
<b>12. VALIDATION</b>						
<b>12.1 Validation Policy</b>						
12.10	The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.					
12.11	The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:					
12.11.1	Defining the DS/DI in terms of its critical product attributes					
12.11.2	Identifying process parameters that could affect the critical quality attributes of the DS/DI					
12.11.3	Determining the range for each critical process parameter expected to be used during routine manufacturing and process control.					
12.12	Validation should extend to those operations determined to be critical to the quality and purity of the DS/DI.					
<b>12.2 Validation Documentation</b>						
12.20	A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.					

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12.21	The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.					
12.22	A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.					
12.23	Any variations from the validation protocol should be documented with appropriate justification.					
<b>12.3 Qualification</b>						
12.30	Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:					
12.30.1	Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.					
12.30.2	Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.					
12.30.3	Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.					
12.30.4	Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.					
<b>12.4 Approaches to Process Validation</b>						
12.40	Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or DS/DI meeting its predetermined specifications and quality attributes.					
12.41	There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.					
12.42	Prospective validation should normally be performed for all DS/DI processes as defined in 12.12. Prospective validation performed on an DS/DI process should be completed before the commercial distribution of the final drug product manufactured from that DS/DI.					
12.43	Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of DS/DI batches have been produced, DS/DI batches are produced infrequently, or DS/DI batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the DS/DI batches.					
12.44	An exception can be made for retrospective validation for well established processes that have been used without significant changes to DS/DI quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:					
12.44.1	Critical quality attributes and critical process parameters have been identified					
12.44.2	Appropriate in-process acceptance criteria and controls have been established					
12.44.3	There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability					
12.44.4	Impurity profiles have been established for the existing DS/DI.					
12.45	Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.					
<b>12.5 Process Validation Program</b>						
12.50	The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex DS/DI processes or DS/DI processes with prolonged completion times). For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.					

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12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.					
12.52 Process validation should confirm that the impurity profile for each DS/DI is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.					
<b>12.6 Periodic Review of Validated Systems</b>					
12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.					
<b>12.7 Cleaning Validation</b>					
12.70 Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to DS/DI quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.					
12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various DS/DIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or DS/DI can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.					
12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.					
12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).					
12.74 Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the DS/DI or its most deleterious component.					
12.75 Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the DS/DI, or other processes where such contamination could be of concern (e.g., non-sterile DS/DIs used to manufacture sterile products).					
12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.					
<b>12.8 Validation of Analytical Methods</b>					
12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.					
12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the DS/DI production process.					
12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.					
12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.					
<b>13. CHANGE CONTROL</b>					

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GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (-/= YES)
13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or DS/DI.					
13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.					
13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the quality unit(s).					
13.13 The potential impact of the proposed change on the quality of the intermediate or DS/DI should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgement should determine what additional testing and validation studies are appropriate to justify a change in a validated process.					
13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.					
13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.					
13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or DS/DI produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.					
13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the DS/DI.					
<b>14. REJECTION AND RE-USE OF MATERIALS</b>					
<b>14.1 Rejection</b>					
14.10 Intermediates and DS/DIs failing to meet established specifications should be identified as such and quarantined. These intermediates or DS/DIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.					
<b>14.2 Reprocessing</b>					
14.20 Introducing an intermediate or DS/DI, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.					
14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.					
14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or DS/DI is not adversely impacted due to the potential formation of by-products and over-reacted materials.					
<b>14.3 Reworking</b>					
14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.					
14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.					
14.32 Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.					
<b>14.4 Recovery of Materials and Solvents</b>					



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14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or the DS/DI is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.					
14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or co-mingling with other approved materials.					
14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.					
14.43 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.					
<b>14.5 Returns</b>					
14.50 Returned intermediates or DS/DIs should be identified as such and quarantined.					
14.51 If the conditions under which returned intermediates or DS/DIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or DS/DIs should be reprocessed, reworked, or destroyed, as appropriate.					
14.52 Records of returned intermediates or DS/DIs should be maintained. For each return, documentation should include:					
14.52.1 Name and address of the consignee					
14.52.2 Intermediate or DS/DI, batch number, and quantity returned					
14.52.3 Reason for return					
14.52.4 Use or disposal of the returned intermediate or DS/DI					
<b>15. COMPLAINTS AND RECALLS</b>					
15.10 All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.					
15.11 Complaint records should include:					
15.11.1 Name and address of complainant					
15.11.2 Name (and, where appropriate, title) and phone number of person submitting the complaint					
15.11.3 Complaint nature (including name and batch number of the DS/DI)					
15.11.4 Date complaint is received					
15.11.5 Action initially taken (including dates and identity of person taking the action)					
15.11.6 Any follow-up action taken					
15.11.7 Response provided to the originator of complaint (including date response sent)					
15.11.8 Final decision on intermediate or DS/DI batch or lot					
15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.					
15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or DS/DI should be considered.					
15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.					
15.15 In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (-/= YES)
<b>ON-SITE AUDIT CHECKLIST</b>					
<b>16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)</b>					
16.10 All contract manufacturers (including laboratories) should comply with the GMP defined in this Guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.					
16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.					
16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.					
16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.					
16.14 Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.					
16.15 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.					
16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.					
<b>17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS</b>					
<b>17.1 Applicability</b>					
17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute or store an DS/DI or intermediate.					
17.11 All agents, brokers, traders, distributors, repackers, and relabelers should comply with GMP as defined in this Guide.					
<b>17.2 Traceability of Distributed DS/DIs and Intermediates</b>					
17.20 Agents, brokers, traders, distributors, repackers, or relabelers should maintain complete traceability of DS/DIs and intermediates that they distribute. Documents that should be retained and available include:					
17.20.1 Identity of original manufacturer					
17.20.2 Address of original manufacturer					
17.20.3 Purchase orders					
17.20.4 Bills of lading (transportation documentation)					
17.20.5 Receipt documents					
17.20.6 Name or designation of DS/DI or intermediate					
17.20.7 Manufacturer's batch number					
17.20.8 Transportation and distribution records					
17.20.9 All authentic Certificates of Analysis, including those of the original manufacturer					
17.20.10 Retest or expiry date					
<b>17.3 Quality Management</b>					
17.30 Agents, brokers, traders, distributors, repackers, or relabelers should establish, document and implement an effective system of managing quality, as specified in Section 2.					

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<b>17.4 Repackaging, Relabeling and Holding of DS/DIs and Intermediates</b>					
17.40 Repackaging, relabeling and holding of DS/DIs and intermediates should be performed under appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and loss of DS/DI or intermediate identity or purity.					
17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.					
<b>17.5 Stability</b>					
17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the DS/DI or intermediate is repackaged in a different type of container than that used by the DS/DI or intermediate manufacturer.					
<b>17.6 Transfer of Information</b>					
17.60 Agents, brokers, distributors, repackers, or relabelers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.					
17.61 The agent, broker, trader, distributor, repacker, or relabeler who supplies the DS/DI or intermediate to the customer should provide the name of the original DS/DI or intermediate manufacturer and the batch number(s) supplied.					
17.62 The agent should also provide the identity of the original DS/DI or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original DS/DI or intermediate manufacturer. (In this context "authorized" refers to authorized by the manufacturer.)					
17.63 The specific guidance for Certificates of Analysis included in Section 11.4 should be met.					
<b>17.7 Handling of Complaints and Recalls</b>					
17.70 Agents, brokers, traders, distributors, repackers, or relabelers should maintain records of complaints and recalls, as specified in Section 15, for all complaints and recalls that come to their attention.					
17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabelers should review the complaint with the original DS/DI or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this DS/DI or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.					
17.72 Where a complaint is referred to the original DS/DI or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabelers should include any response received from the original DS/DI intermediate manufacturer (including date and information provided).					

## 21. | Legal Notices

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