

NOTICE

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

The Drug Substance Supplier Qualification Program involves Good Manufacturing Practices (GMP) auditing and testing for conformity. USP's intention is to provide guidance and direction to manufacturers of drug substances and users of drug substances used in the pharmaceutical industry to assist them in complying with the USP Drug Substance SQP requirements. USP considers this a cooperative effort between USP and the manufacturers and the users. USP encourages manufacturers and users of drug substances to provide input, based on their needs and experience, to help shape the future direction and requirements of the USP Drug Substance SQP. Barring safety concerns or other special circumstances, USP maintains the confidentiality of information gained through the qualification process in accordance with the provisions of the program Agreement.

TABLE OF CONTENTS

	NOTICE.....	i
1.	OVERVIEW.....	2
2.	CRITERIA FOR PARTICIPATION	4
3.	REQUIRED PROCESS AND SUBMISSIONS	5
4.	PROCESS FLOW CHART.....	7
5.	DRUG SUBSTANCE ACCEPTANCE USP-DRUG SUBSTANCE SQP	8
6.	EVALUATION OF PRE-AUDIT DOCUMENTATION	9
7.	SUBMISSION OF DRUG SUBSTANCE SAMPLES	11
8.	TESTING OF DRUG SUBSTANCE SAMPLES	12
9.	SPECIFICATIONS FOR DRUG SUBSTANCE	13
10.	ON-SITE AUDIT CRITERIA.....	16
11.	USP-DRUG SUBSTANCE SQP REPORT OF FINDINGS	19
12.	ISSUANCE AND USE OF THE QUALIFICATION STATUS.....	21
13.	GLOSSARY.....	22
14.	FORMS AND CHECKLISTS	26
	• Pre-Audit Documentation Checklist	
	• On-Site Audit Checklist	
15.	LEGAL NOTICES.....	59

1. OVERVIEW

The United States Pharmacopeia's Drug Substance Supplier Qualification Program (USP Drug Substance SQP) is a public health program of the United States Pharmacopeia (USP). Participation is voluntary and open to pharmaceutical companies that use drug substances and require qualification of their drug substance vendors.

The USP Drug Substance SQP covers drug substances used in the manufacture of pharmaceutical products.

The USP Drug Substance SQP includes:

- Evaluation of suppliers' 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*).
- Testing for compliance with *USP-NF*, *EP* and/or *JP* monographs, as applicable. In addition, testing for the drug product manufacturer's additional specifications, if any.
- Laboratory testing of drug substance samples from selected batches for compliance with the supplier's specification for the drug substance.
- Issuance of a letter to the participant, indicating the supplier's USP Drug Substance SQP qualification status.

Successful qualification of a drug substance supplier provides assurance that:

- The supplier's quality system helps to ensure that the drug substance being supplied meets its specification for identification, strength, purity, and quality, and that it is consistent in quality from batch to batch.
- The drug substance is prepared under accepted good manufacturing practices.
- The drug substance meets compendial and/or drug product manufacturer's own purchase specification, including requirements for acceptable limits of contaminants and impurities.

Thus, the USP Drug Substance SQP offers users of drug substances a trusted means of qualifying the suppliers of drug substances used in the manufacture of drug products.

Since 1820, the **United States Pharmacopeia (USP)** has been a trusted and recognized source of standards for the identification, strength, quality, and purity of medicines, dietary supplements, and related products. These standards are developed by a unique process involving all interested parties and are accepted by many countries worldwide.

USP is a non-governmental, not-for-profit organization with a mission to promote quality in public health. Scientific experts and other individuals representing numerous fields including pharmacy,

UNITED STATES PHARMACOPEIA Drug Substance Supplier Qualification Program

medicine, and other health care professions; academia; the U.S. Government; the pharmaceutical industry; the dietary supplement industry; and consumer organizations, volunteer their efforts to support USP's work.

The USP Drug Substance SQP is a natural progression of USP's long history of establishing officially recognized public standards for drug substances, drug products, biologics, biotechnologically derived products, medical devices, dietary supplements, and excipients. Please visit www.usp.org to learn more about USP.

2 | CRITERIA FOR PARTICIPATION

Drug product manufacturers participating in the USP Drug Substance SQP agree to:

- Complete the program Agreement in cooperation and collaboration with the drug substance supplier(s).
- Work with the drug substance supplier(s) to eliminate the need for USP to sign a confidentiality agreement with the drug substance supplier(s).
- Work with the drug substance supplier(s) to submit any requested data, documentation.
- Collaborate with the drug substance supplier(s) to subject the supplier's drug substance(s) and facilities to all testing and audits specified in the program.
- Abide by the decisions made in accordance with the rules and requirements of the USP Drug Substance SQP.
- Operate in accordance with the provisions of relevant federal regulations.
- Pay all fees required by USP agreements or by documents executed between the drug product manufacturer and USP.

3 | REQUIRED PROCESS AND SUBMISSIONS

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

Drug Product Manufacturers that wish to participate in the USP Drug Substance SQP shall:

- Appoint a duly authorized representative to execute a program Agreement.
- Provide the name and address of the supplier(s) of the drug substances for which qualification is sought, with batch history for not less than ten (10) batches of the drug substances or batches manufactured dating back one year (if available), whichever comes first for the drug substance, manufactured under the supplier's current quality system.
- Work with the supplier(s) to provide USP Drug Substance SQP with representative sample aliquots of the drug substance(s) as specified by USP Drug Substance SQP staff.
- Work with the supplier(s) to submit the following documentation as described in this Manual for Participants:
 1. Pre-Audit documentation (see Forms and Checklist, section 14.
 2. Toxicology data: submission of toxicology data is not necessary if the drug substance is used in an FDA approved drug product or in a drug product approved for marketing in an 802 country¹. For all other drug substances, toxicology data demonstrating that the article is safe for human use must be included in the submitted documentation. These data will be evaluated by the appropriate USP Expert Committee.¹
 3. Drug substance release: specification (physical, chemical, and microbiological tests, analytical procedures, and acceptance criteria) and test results for the three batches of the drug substance(s) selected for testing in USP laboratories.
 4. Drug substance in-line, on-line, and at-line tests when used for release.

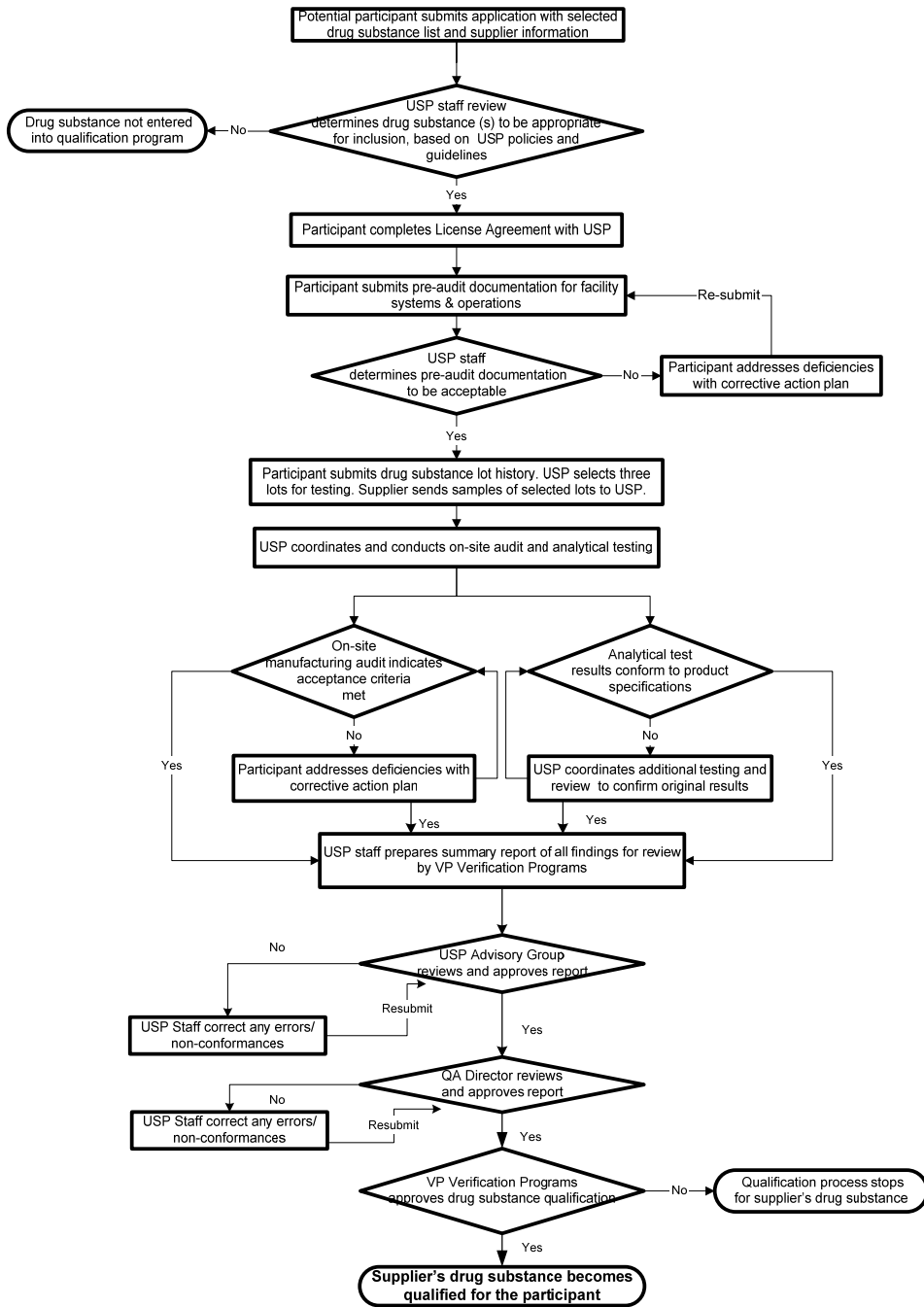
¹ 802 country: A country that is recognized under section 802(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act and to which a drug or device may be exported, without having the drug or device approved by the U.S. Food and Drug Administration, if the drug or device complies with the laws of that country 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.

UNITED STATES PHARMACOPEIA Drug Substance Supplier Qualification Program

5. An executed batch record for one of the three batches of the drug substance(s) selected for testing in USP laboratories. Under some circumstances, the USP auditor may be asked to review the executed batch sheet during on-site audit.
6. Packaging and labeling records for the three batches of the drug substance(s) selected for testing in USP laboratories.

4. PROCESS FLOW CHART

Drug Substance SQP Process



5. DRUG SUBSTANCE ACCEPTANCE INTO USP DRUG SUBSTANCE SQP

Upon completion of the program Agreement, the drug product manufacturer submits to USP Drug Substance SQP a list of drug substances for which supplier qualification is sought. USP Drug Substance SQP 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 Drug Substance SQP the drug substance batch history (batch number, description of the batch number coding system, date of manufacture, manufacturing facility, and batch size) for not less than ten (10) batches of the drug substances or batches manufactured dating back one year (if available), whichever comes first for the drug substance, for which supplier qualification is sought that have been manufactured under the supplier's current quality systems. Also, the participant submits the list of lots recalled, if any, in the past five years for the drug substance(s) under consideration.

Drug substances which are used in FDA approved drug products or in drug products approved by an "802" country are on the current "Approved" list for inclusion in the USP Drug Substance SQP.

All other drug substances will require an evaluation, with the established criteria for inclusion, before the drug substance can be included in the USP Drug Substance SQP.

6. EVALUATION OF PRE-AUDIT DOCUMENTATION

The Checklist for Pre-Audit Documentation (see Forms and Checklists, section 14) is used by USP Drug Substance SQP as a tool to ascertain information about the drug substance supplier, its quality systems, and critical manufacturing information.

The supplier, working with the Participant, should provide the information listed on the Checklist for Pre-Audit Documentation to USP Drug Substance SQP. Upon receipt of the form and information, USP Drug Substance SQP staff will perform a preliminary review of the information. If additional information is required, USP Drug Substance SQP staff will inform the drug substance supplier; such information should be submitted within 30 calendar days.

Note that the requested information must be submitted in the format indicated on the Checklist for Pre-Audit Documentation (section 14). The requested information should be submitted electronically. If electronic submission is not feasible, then the information may be submitted in a three ring binder. Complete documentation must be received before the review and audit process can begin.

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 drug substance supplier from consideration for qualification until the deficiencies are corrected.

UNITED STATES PHARMACOPEIA Drug Substance Supplier Qualification Program

- Flow diagram(s) of manufacturing process
- Manufacturer(s)
- Quality management
- Personnel
- Building and facilities site/building map
- Process equipment
- Documentation and records
- Materials management
- Production and in-process controls
- Packaging and identification labeling of ingredients and intermediates
- Storage and distribution
- Laboratory controls
- Validation
- Change control
- Rejection and re-use of materials
- Complaints and recalls
- Contract manufacturers and laboratories
- Agents, brokers, traders, distributors, repackers, and relabelers

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

Deficiencies, if any, will be noted, and provided to the supplier. The supplier should develop a corrective action plans within 30 calendar days of receipt of the notification. USP Drug Substance SQP 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 Drug Substance SQP, the qualification process will proceed. If the drug substance supplier fails to develop and implement corrective action, the qualification process will be discontinued.

7 | SUBMISSION OF DRUG SUBSTANCE SAMPLES

For a supplier for which a drug product manufacturer is seeking qualification, USP Drug Substance SQP will select the batches to be subjected to testing during the qualification process. This decision will be based in part on the batch history for the drug substances and the availability of the drug substance batches for sampling. The batches selected will be from those manufactured on the regular commercial scale. No batches manufactured under pilot scale or R&D scale will be accepted.

USP Drug Substance SQP will select, at minimum, three drug substance batches for each drug substance for which qualification of the supplier is being sought.

USP Drug Substance SQP will request that the drug product manufacturer obtain or arrange with the drug substance supplier to provide representative sample aliquots of the drug substance batches and ship them via the most expedient and appropriate courier services to the testing site identified by USP Drug Substance SQP. Alternatively, USP Drug Substance SQP may decide to send a USP Drug Substance SQP representative to observe the sampling.

Drug substance batches should be sampled according to the supplier'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:

- Company Name
- Drug Substance Name
- Drug Substance Item Code Number
- Drug Substance Batch Number
- Date Sampled
- Sampler's Initials
- Quantity of Drug Substance

The supplier may be required to send sufficient quantity of samples, divided into two separate container closure systems and labeled appropriately as indicated above, for chemical and microbiological analysis.

8 | TESTING OF DRUG SUBSTANCE SAMPLES

Drug substances will be tested for critical quality attributes and include both chemical and microbiological tests, as determined by USP Drug Substance SQP to evaluate the quality of the drug substance and its conformance to the supplier's specification and certificate of analysis, as well as to USP, EP, and/ JP compendia, and the drug product manufacturer's specifications, where applicable.

Please refer to section 9 "SPECIFICATIONS FOR DRUG SUBSTANCE" for further details on testing of drug substance samples.

USP will coordinate testing of drug substance samples in the USP laboratories and/or by one or more approved contract testing 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 drug substance supplier.

If the test data obtained conform to the acceptance criteria and there are no other issues arising from the test results, USP Drug Substance SQP will proceed with the qualification 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 Drug Substance SQP 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, the reanalyzed results will be averaged and reported.

In the case of nonconforming results, in which 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 batch, 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 result will be compared to the drug substance supplier's acceptance criteria for determining compliance to the specification and or certificate of analysis claim(s). In the event of a question regarding compliance to the drug substance supplier's specification and/or certificate of analysis, the decision by USP Drug Substance SQP shall be final.

9. SPECIFICATIONS FOR DRUG SUBSTANCE

A specification is defined as the list of tests, analytical test 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 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 suitability of the material for its intended use. (See ICH Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Including Decision Trees.)*)

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 its shelf-life or retest date 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 during the on-site audit.

The following "Universal" 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 should be included.
- (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-NF* General Chapter <467> *Residual Solvents* should be employed, and the content of residual solvents in the drug substance should be evaluated and justified.

The applicability of the following "Specific" tests depends on the nature of the drug substances and its intended use in drug products.

(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, etc. 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: some 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, 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-NF* General Chapter <561> *Articles of Botanical Origin* and should comply with the applicable Federal regulations in the United States, or with the requirements of the appropriate government body.

(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 (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., *USP-NF* General Chapter <61> *Microbial Limit Tests*).

For questions or clarification regarding specifications for raw materials and/or drug substances, please contact the USP Drug Substance SQP staff at 301.816.8273.

10. ON-SITE AUDIT CRITERIA

USP staff auditors and/or approved contract auditors perform the on-site audit of the supplier's facilities and operations. In general, suppliers will conduct internal audits on an annual basis after successfully completing all aspects of the Program. 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 11 USP DRUG SUBSTANCE SQP REPORT OF FINDINGS.

In consultation with the drug product manufacturer, the audit may be performed with notice at a date and time mutually agreed upon by USP and the supplier, or the audit may be performed unannounced. For scheduled audits, USP will communicate to the supplier's designated contact person the agenda for the audit specifying all relevant areas to be covered. The supplier must assure the availability of the required personnel. Whether announced or unannounced, the ICH Q7 *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* principles will be followed. Safety procedures for the areas being audited will be followed.

Auditors will apply the following criteria: (Please See Forms and Checklists, section 14 for the complete list)

Quality Management

- Dedicated Quality Assurance/Quality Control department.
- System to ensure drug substance quality prior to release.
- Program for internal audits.
- Product quality review.

Personnel

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

Buildings and Facilities

- Adequate security to prevent access for unauthorized personnel.
- Adequate design and construction of facility.

Process Equipment

- Adequate design and construction of equipment used in manufacturing.
- Maintenance, cleaning and calibration of equipment to ensure consistent performance for its intended use.
- Electronic records, computerized systems, including proof of performance, appropriate security and backup.

Documentation and Records

- Program for control of all documentation related to the manufacture of drug substances
- Procedures for reviewing, approving, distributing, revising and archiving documentation and records
- Documentation of equipment cleaning and use
- Records for raw materials, intermediates, labeling and packaging materials
- Master production records and executed batch production records
- Laboratory control records

Materials Management

- Program for receipt, quarantine, disposition, release, retain, and distribution of incoming raw materials.
- Sampling and testing of incoming production materials
- Proper storage conditions
- System of material reconciliation

Production and In-process Controls

- Adequate controls for raw material weighing and handling
- Time limits for manufacturing operations
- In-process sampling and controls
- Procedures for blending batches of intermediates or drug substances, if applicable
- Adequate procedures to prevent cross contamination

Packaging and Identification Labeling

- Program for controlling packaging and labeling materials
- Procedures to ensure correct packaging materials are used
- Procedures for label issuance and control

Storage and Distribution

- Storage of materials under appropriate conditions
- Procedures for distribution and traceability of intermediates and drug substances

Laboratory Controls

- Written specifications, sampling plan and test procedures for drug substances
- Appropriate maintenance and calibration of laboratory equipment/instruments
- Proper use and control of reference standards and reagents.
- Use of validated/qualified and appropriate test procedures
- Out of specification (OOS) policy and procedures
- Issuance of certificate of analysis for each batch of intermediate or drug substance
- Stability monitoring of drug substance for expiry or retest dating

Validation

- Validation policy
- Validation protocols and reports
- Qualification of equipment
- Validation of manufacturing processes
- Validation of cleaning procedures
- Validation of analytical procedures

Change Control

- Formal change control system to evaluate all changes that may affect product quality
- Procedures for identification, documentation, review and approval of changes

Rejection and Re-use of Materials

- Program for quarantining material not meeting established specifications
- Procedures reprocessing, reworking or reusing material, if applicable

Complaints and Recalls

- Program for handling customer complaints
- Procedures for handling recalls

Contract Manufacturers and Laboratories

- Program for evaluating contract manufacturers and laboratories to ensure they comply with GMPs

The on-site audit will be conducted according to the On-Site Audit Checklist (See Forms and Checklists, section 14). 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 supplier along with the Program's report of any actions that the supplier needs to take to correct these deficiencies. The supplier will have 30 calendar days to reply to reported deficiencies with a corrective action plan. Failure to do so may result in the discontinuation of the qualification process. For Action Level 1 deficiencies (see section 11 USP DRUG SUBSTANCE SQP REPORT OF FINDINGS) proof of corrective action, with the date of completion or progress made, must be submitted to USP before the qualification process can continue for the drug substance. A follow up on-site audit may be necessary before the qualification process can continue. For Action Level 2 deficiencies, the qualification process will continue, but deficiencies must be addressed and corrective action taken before the qualification letter can be issued for the drug substance. For Action Level 3 deficiencies, the drug substance manufacturer needs to provide a commitment to address the issues cited with the drug product manufacturer within the specified time period.

11. | USP-DRUG SUBSTANCE SQP REPORT OF FINDINGS

A report will be issued to the drug product manufacturer listing the final determination and status of any issues regarding the various elements of the USP-Drug Substance SQP as it pertains to the drug substance supplier. 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.
- Analytical Results at all stages of manufacture.

The results for the On-Site Audit apply to the manufacturing site audited and the drug substance(s) manufactured at that site, whereas the testing results 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 of the issue or deficiency. All Action Levels require some action to be taken by the company.

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/process. Action Level 1 issues involve changes to the current quality system. Action Level 1 issues must be adequately resolved before qualification can be given to the drug substance supplier, and may require that the supplier's drug substance and manufacturing site be resubmitted for qualification.

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/process. Action Level 2 issues do not involve changes to the current quality system. Action Level 2 issues must be adequately resolved before qualification can be given to the drug substance supplier.

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 minor deficiencies. Action Level 3 issues can be resolved by supplying additional information or by making requested changes to the drug substance/process. Action Level 3 issues would allow the USP Drug Substance SQP qualification to be issued subject to the drug substance supplier's commitment to address the issues cited with the drug product manufacturer within the specified time period.

The status of the pre-audit documentation, on-site audit, and analytical testing 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 and Fail is based on the following determination:

PASS indicates that only Action Level 3 issues or deficiencies need to be resolved. It is required that a commitment to resolve all Action Level 3 items with the drug product manufacturer within the specified time period be provided by the drug substance supplier prior to USP Drug Substance SQP awarding qualified drug substance supplier status.

FAIL indicates that one or more Action Level 1 or Action Level 2 issues or deficiencies need to be resolved. The drug substance supplier would need to make the appropriate change(s) to the drug substance/process and most likely may require that the supplier's drug substance and manufacturing site be resubmitted for qualification.

Any major, moderate and minor change, or any other criteria deemed by the drug substance supplier to be essential or significant, should be immediately be reported in writing to the drug product manufacturer who sponsored the qualification.

After USP Drug Substance SQP has given qualification status to a drug substance supplier, any major, moderate and minor changes to a drug substance's specification, process control data, raw material source, equipment, manufacturing site change, testing, or any other essential or significant criteria invalidates the supplier qualification status, until such time that the changes can be evaluated by USP at the request of the drug product manufacturer.

Disclaimer

The drug substance supplier understands that compliance with USP-Drug Substance SQP does not constitute compliance with U.S. federal, state, local, or foreign country requirements. The drug substance supplier agrees that any sampling, inspections, or tests conducted by USP-Drug Substance SQP are designed only to verify compliance with USP-Drug Substance SQP requirements and do not relieve the drug substance supplier of its responsibility to ensure the quality of its drug substances in the marketplace or to comply with applicable federal, state, local, or foreign country regulations. Compliance with USP Drug Substance SQP may not be used as a defense when compliance with legal requirements is an issue. The drug substance supplier agrees that USP will not be called to testify or otherwise appear on its behalf in any regulatory or other legal proceeding brought by a regulatory agency. USP is not an agent of the drug substance supplier or acting in capacity thereof.

12. ISSUANCE AND USE OF THE QUALIFICATION STATUS

On satisfactory completion of the:

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

Formal notification of supplier qualification status will be made by USP Drug Substance SQP to the drug product manufacturer in writing. The notification will specify which of the drug substance supplier's drug substance(s) are included in the qualification of the manufacturing site and other limiting information as appropriate. The qualification status is only applicable to drug substances supplied from the manufacturing site to the drug product manufacturer who engaged the Program in regard to a particular drug substance supplier. The qualification status is not applicable to drug substances sold by the drug substance supplier to other drug product manufacturers.

Participants and drug substance suppliers are reminded, however, that the terms and conditions set forth in the USP Drug Substance SQP Agreement have precedence over this manual.

13. GLOSSARY

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. 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.

Agreement: an agreement between USP and the drug product manufacturer who enters into agreement with USP seeking the services of USP to qualify their drug substance supplier.

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

Council of Experts (CoE): the elected chairs of Expert Committee.

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 company official has submitted fraudulent documents to the USP Drug Substance SQP 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 company, affiliates, or agents engage in violation of any USP Drug Substance SQP 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.

Drug Substance SQP: Drug Substance Supplier Qualification Program

EP: European Pharmacopoeia.

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

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 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.

Participant: a company that has qualified to participate in the USP Drug Substance SQP.

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 company's removal or correction of its marketed drug substance that the USP Drug Substance SQP, an official organization such as the FDA, or the company 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-NF* 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.

Specifications: 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.

14. | FORMS AND CHECKLISTS

- Pre-Audit Documentation Checklist
- On-Site Audit Checklist

Drug Substance Supplier Qualification Pre-Audit Documentation Checklist

Participant Information				
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
Employees				
Total Number	Manufacturing	QC	QA	Other
Ingredients				
List all Ingredients manufactured at site and indicate which ingredients are to be submitted for verification. (Attach additional sheets if necessary.)				
Pre-Audit Documentation				
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			Shaded area to be completed by USP VER Staff (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				
1. Flow Diagram(s) of Manufacturing Process: <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
2. Manufacturer(s) <i>The name, exact address, and responsibility of each manufacturer, including contractors, and each proposed production site of facility involved in manufacturing and testing</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
2. Quality Management: <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
3. Personnel: <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
4. Building and Facilities Site/Building Map: <i>Design and Construction, Utilities, Water, Containment, Lighting, Sewage and Refuse, Sanitation and Maintenance</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
5. Process Equipment: <i>Design and Construction, Equipment Maintenance, and Cleaning Procedures, Calibration, and Computerized systems</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
6. Documentation and Records: <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
7. Materials Management: <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
8. Production and In-Process Controls: <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
9. Packaging and Identification Labeling of Ingredients and Intermediates: <i>General Controls, Packaging Materials, Label Issuance and Control, Packaging and Labeling Operations</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
10. Storage and Distribution: <i>Warehouse Procedures, Distribution Procedures</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC
11. Laboratory Controls: <i>General Controls, Testing of Intermediates and Ingredients,</i>			<input type="checkbox"/> AC	<input type="checkbox"/> NAC

Drug Substance Supplier Qualification

On-Site Audit Checklist for Drug Substance (DS)

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 BATCH OF DRUG SUBSTANCE (DS) 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 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)
ON-SITE AUDIT CHECKLIST					
1. INTRODUCTION					
1.1 DSs 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 begins.					
1.3 Brief company history					
1.4 Status of last FDA or other regulatory inspection					
1.5 Other sites/companies involved in operations					
2. QUALITY MANAGEMENT					
2.1 Principles					
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 DSs 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.).					
2.2 Responsibilities of the Quality Unit(s)					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (* = YES)
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 DSs. 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 for distribution					
2.22.4 Making sure that critical deviations are investigated and resolved					
2.22.5 Approving all specifications and master production instructions					
2.22.6 Approving all procedures impacting the quality of intermediates or DSs					
2.22.7 Making sure that internal audits (self-inspections) are performed					
2.22.8 Approving intermediate and DS contract manufacturers					
2.22.9 Approving changes that potentially impact intermediate or DS 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 DSs and/or intermediates where appropriate					
2.22.15 Performing product quality reviews (as defined in Section 2.5)					
2.3 Responsibility for Production Activities					
2.3.1 Preparing, reviewing, approving and distributing the instructions for the production of intermediates or DSs according to written procedures					
2.3.2 Producing DSs 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					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
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.					
2.4 Internal Audits (Self Inspection)					
2.40 In order to verify compliance with the principles of GMP for DSs, 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.					
2.5 Product Quality Review					
2.50 Regular quality reviews of DSs 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 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.					
3. PERSONNEL					
3.1 Personnel Qualifications					
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.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
ON-SITE AUDIT CHECKLIST					
3.2 Personnel Hygiene					
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 DSs.					
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.					
3.3 Consultants					
3.30 Consultants advising on the manufacture and control of intermediates or DSs 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.					
4. BUILDINGS AND FACILITIES					
4.1 Design and Construction					
4.10 Buildings and facilities used in the manufacture of intermediates and DSs 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.					
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 DSs					
4.14.3 Sampling of intermediates and DSs					
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					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
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.					
4.2 Utilities					
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 DSs 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.					
4.24 Drains should be of adequate size and should be provided with an air break.					
4.3 Water					
4.30 Water used in the manufacture of DSs 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 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 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.					
4.4. Containment					
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.					
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 DSs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from DSs.					

GMP ITEM	ON-SITE AUDIT CHECKLIST				ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (* = YES)
4.5 Lighting									
4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.									
4.6 Sewage and Refuse									
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.									
4.7 Sanitation and Maintenance									
4.70 Buildings used in the manufacture of intermediates and DSs 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 DSs.									
5. PROCESS EQUIPMENT									
5.1 Design and Construction									
5.10 Equipment used in the manufacture of intermediates and DSs 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 DSs do not alter the quality of the intermediates DSs 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 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 DSs 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).									
5.2 Equipment Maintenance and Cleaning									

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (* = YES)
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 DSs. 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 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.					
5.3 Calibration					
5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or DSs 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(s) manufactured using this equipment since the last successful calibration.					
5.4 Computerized Systems					
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.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (* = YES)
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.					
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 DSs 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.					
6. DOCUMENTATION AND RECORDS					
6.1 Documentation System and Specifications					
6.10 All documents related to the manufacture of intermediates or DSs 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 DSs 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.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
6.17 Specifications should be established and documented for raw materials, intermediates where necessary, DSs, 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 DSs 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.					
6.2 Equipment Cleaning and Use Record					
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, then individual equipment records are not necessary if batches of the intermediate or DS 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.					
6.3 Records of Raw Materials, Intermediates, DS Labeling and Packaging Materials					
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'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 labeling and packaging materials for conformity with established specifications					
6.30.5 The final decision regarding rejected raw materials, intermediates or DS labeling and packaging materials.					
6.31 Master (approved) labels should be maintained for comparison to issued labels.					
6.4 Master Production Instructions (Master Production and Control Records)					
6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and DS 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 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:					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (* = YES)
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 to assure its suitability for use, including the labeling and packaging materials and special storage conditions with time limits, where appropriate.					
6.5 Batch Production Records (Batch Production and Control Records)					
6.50 Batch production records should be prepared for each intermediate and DS 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:					
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					
6.52.10 Representative label of DS 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 to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.					
6.6 Laboratory Control Records					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
ON-SITE AUDIT CHECKLIST					
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 DSs					
6.61.4 Out-of-specification (OOS) investigations					
6.7 Batch Production Record Review					
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 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 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).					
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.					
7. MATERIALS MANAGEMENT					
7.1 General Controls					
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 DSs 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).					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
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 manufacturer.					
7.14 Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.					
7.2 Receipt and Quarantine					
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.					
7.3 Sampling and Testing of Incoming Production Materials					
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.					
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.					
7.4 Storage					
7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
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.					
7.5 Re-evaluation					
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).					
8. PRODUCTION AND IN-PROCESS CONTROLS					
8.1 Production Operations					
8.10 Raw materials for intermediate and DS 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.					
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.					
8.2 Time Limits					
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 DSs. 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.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
ON-SITE AUDIT CHECKLIST					
8.3 In-process Sampling and Controls					
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 DSs. 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 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 DSs. 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 DSs. 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.					
8.4 Blending Batches of Intermediates or DSs					
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. 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 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 are critical (e.g., DSs 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.					
8.5 Contamination Control					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
8.50 Residual materials can be carried over into successive batches of the same intermediate or DS 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 impurity profile.					
8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or DSs by other materials.					
8.52 Precautions to avoid contamination should be taken when DSs are handled after purification.					
9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES					
9.1 General					
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.					
9.2 Packaging Materials					
9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or DS 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, 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 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.					
9.3 Label Issuance and Control					
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.					
9.4 Packaging and Labeling Operations					
9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
9.41 Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or DSs.					
9.42 Labels used on containers of intermediates or DSs 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.					
9.43 If the intermediate or DS 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 DSs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or DSs 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 DSs 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.					
9.46 Intermediate or DS 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.					
10. STORAGE AND DISTRIBUTION					
10.1 Warehousing Procedures					
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.					
10.2 Distribution Procedures					
10.20 DSs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). DSs 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 DSs 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 or intermediate should be stated on the label.					
10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the DS 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 can be readily determined to permit its recall.					
11. LABORATORY CONTROLS					
11.1 General Controls					
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.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
11.12 All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, DSs, 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 DSs 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 has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the DS 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.					
11.17 Primary reference standards should be obtained as appropriate for the manufacture of DSs. 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.					
11.2 Testing of Intermediates and DSs					
11.20 For each batch of intermediate and DS, 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. 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. Impurity profiles are normally not necessary for DSs 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 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 where microbial quality is specified.					
11.3 Validation of Analytical Procedures - see Section 12.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
ON-SITE AUDIT CHECKLIST					
11.4 Certificates of Analysis					
11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or DS on request.					
11.41 Information on the name of the intermediate or DS including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or DSs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or DSs 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.					
11.5 Stability Monitoring of DSs					
11.50 A documented, on-going testing program should be designed to monitor the stability characteristics of DSs, 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 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 is expected to remain stable for at least two years, fewer than three batches can be used.					
11.54 Thereafter, at least one batch per year of DS 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 DSs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other DSs 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 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.					
11.6 Expiry and Retest Dating					
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 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 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 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.					

GMP ITEM	ON-SITE AUDIT CHECKLIST				ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (* = YES)
11.7 Reserve/Retention Samples									
11.70	The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of DS and not for future stability testing purposes.								
11.71	Appropriately identified reserve samples of each DS 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 DSs 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 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.								
12. VALIDATION									
12.1 Validation Policy									
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 in terms of its critical product attributes								
12.11.2	Identifying process parameters that could affect the critical quality attributes of the DS								
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.								
12.2 Validation Documentation									
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.								
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.								
12.3 Qualification									
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:								

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
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.					
12.4 Approaches to Process Validation					
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 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 processes as defined in 12.12. Prospective validation performed on an DS process should be completed before the commercial distribution of the final drug product manufactured from that DS.					
12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of DS batches have been produced, DS batches are produced infrequently, or DS 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 batches.					
12.44 An exception can be made for retrospective validation for well established processes that have been used without significant changes to DS 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.					
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.					
12.5 Process Validation Program					
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 processes or DS 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.					
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.					

GMP ITEM	ON-SITE AUDIT CHECKLIST				ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (* = YES)
12.52 Process validation should confirm that the impurity profile for each DS 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.									
12.6 Periodic Review of Validated Systems									
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.									
12.7 Cleaning Validation									
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 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 DSs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or DS 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 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, or other processes where such contamination could be of concern (e.g., non-sterile DSs 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.									
12.8 Validation of Analytical Methods									
12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia 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 production process.									

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
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.					
13. CHANGE CONTROL					
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.					
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 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 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.					
14. REJECTION AND RE-USE OF MATERIALS					
14.1 Rejection					
14.10 Intermediates and DSs failing to meet established specifications should be identified as such and quarantined. These intermediates or DSs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.					
14.2 Reprocessing					
14.20 Introducing an intermediate or DS, 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 is not adversely impacted due to the potential formation of by-products and over-reacted materials.					

GMP ITEM	ON-SITE AUDIT CHECKLIST				ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
14.3 Reworking									
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.									
14.4 Recovery of Materials and Solvents									
14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or the DS 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.									
14.5 Returns									
14.50 Returned intermediates or DSs should be identified as such and quarantined.									
14.51 If the conditions under which returned intermediates or DSs 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 DSs should be reprocessed, reworked, or destroyed, as appropriate.									
14.52 Records of returned intermediates or DSs should be maintained. For each return, documentation should include:									
14.52.1 Name and address of the consignee									
14.52.2 Intermediate or DS, batch number, and quantity returned									
14.52.3 Reason for return									
14.52.4 Use or disposal of the returned intermediate or DS									
15. COMPLAINTS AND RECALLS									
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									

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (= YES)
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)					
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 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 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.					
16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)					
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.					
17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS					
17.1 Applicability					
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 or intermediate.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (* = YES)
17.11 All agents, brokers, traders, distributors, repackers, and relabelers should comply with GMP as defined in this Guide.					
17.2 Traceability of Distributed DSs and Intermediates					
17.20 Agents, brokers, traders, distributors, repackers, or relabelers should maintain complete traceability of DSs 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 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					
17.3 Quality Management					
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.					
17.4 Repackaging, Relabeling and Holding of DSs and Intermediates					
17.40 Repackaging, relabeling and holding of DSs and intermediates should be performed under appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and loss of DS or intermediate identity or purity.					
17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.					
17.5 Stability					
17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the DS or intermediate is repackaged in a different type of container than that used by the DS or intermediate manufacturer.					
17.6 Transfer of Information					
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 or intermediate to the customer should provide the name of the original DS or intermediate manufacturer and the batch number(s) supplied.					

GMP ITEM	ACCEPTABLE	NOT ACCEPTABLE	NOT APPLICABLE	NOT REVIEWED	COMMENTS OR ATTACHMENTS (N= YES)
17.62 The agent should also provide the identity of the original DS 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 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.					
17.7 Handling of Complaints and Recalls					
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 or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this DS 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 or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabelers should include any response received from the original DS intermediate manufacturer (including date and information provided).					

15. | LEGAL NOTICES

The information in this manual, including but not limited to text and images herein and their arrangement, is copyrighted. Copyright 2008 The United States Pharmacopeial Convention. All rights reserved.

This manual is provided for informational purposes only. It does not constitute a legal and binding contract between USP and the participant. In the event of a conflict between this manual and the program Agreement, the terms and conditions of the program Agreement shall take precedence over the terms and conditions of this manual.

USP does not endorse, guarantee, or warrant the goods and services offered by Program participants. The program Agreement provides that USP shall not be liable for any damages whatsoever, including bodily harm and/or property damage that may result from a drug substance of a participant verified in the Program. USP reserves the right to change or terminate the Program at any time without notice. USP reserves the right to disqualify participants that fail to comply with any of the Program's requirements from participating in the Program.