

STANDARD OPERATING PROCEDURE
International Pharmaceutical Excipients Auditing, Inc.

Title Conducting the Certification Audit		Revision 2	SOP Number 20
Originator Irwin Silverstein	Approved By IPEA Management Committee	Date Approved August 18, 2011	Page Page 1 of 7

PURPOSE:

This procedure describes how an Excipient GMP Conformance Certification audit is conducted at the excipient site of manufacture.

SCOPE:

This procedure applies to all Excipient GMP Conformance Certification audits.

RESPONSIBILITIES:

1. **IPEA Executive Management:** Assure the provisions of this procedure are implemented.
2. **Lead Auditor:** Conduct the site audit according to the guidance provided by this procedure.

REFERENCES:

1. ANSI/ISO/ASQ QE 19011:2008, Guidelines for Management Systems Auditing
2. Form 05: Certification Pre-audit Questionnaire.
3. SOP 1, Auditor Qualification.
4. SOP 14, Application for Certification.
5. SOP 24, Documenting the Certification Audit.
6. *The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients*, 2006

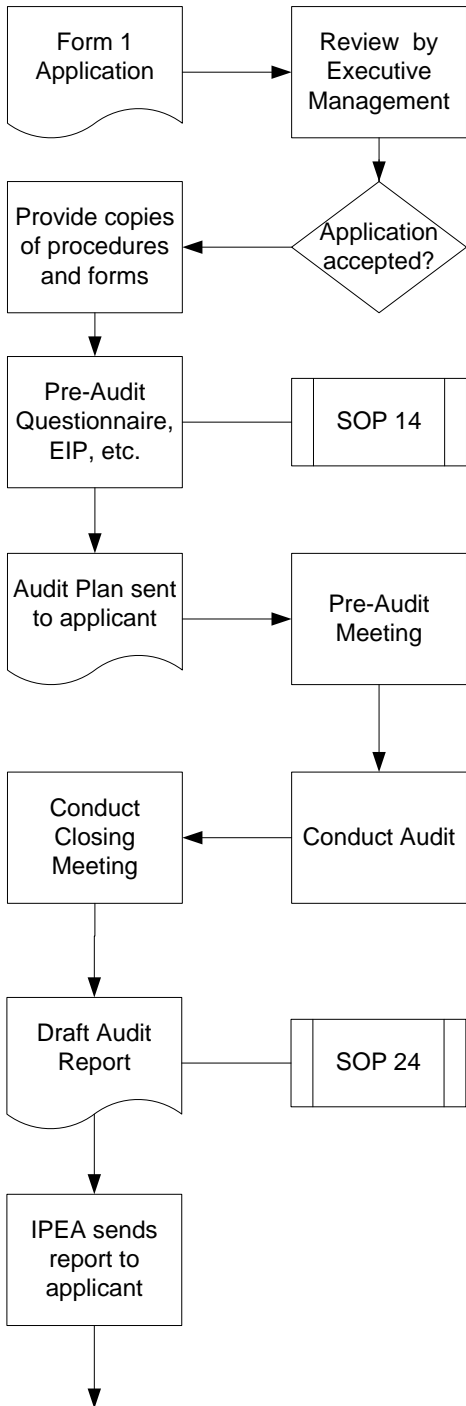
DEFINITIONS:

See Glossary

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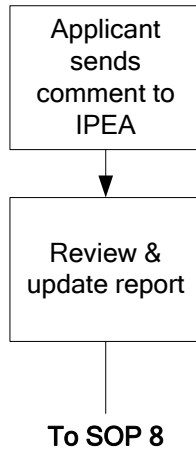
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PROCEDURE:

1. In preparation for the site audit, the Lead Auditor prepares an audit plan based upon the information provided in the pre-audit questionnaire. The audit plan contains:
 - a. **Purpose:** A description of the reason the audit was requested. Ordinarily, the audit will be conducted to gather information concerning the site Quality System conformance to the current Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients.
 - b. **Scope:** The audit plan identifies the excipient ingredients to be assessed during the site visit. The plan lists all grades of the excipient produced at the facility. Where applicable, the plan groups excipients by type such as when the manufacture of multiple excipients use different chemistry, differ in their composition, or are produced in different facilities or equipment.

 The plan includes a list of those operational and functional areas to be visited during the audit including those identified as contract operations within the scope of the Certification.
 - c. **Audit Standard:** The audit plan documents the version of the IPEC excipient audit guide to be used for the assessment.
 - d. **Schedule:** The audit plan lists the proposed timing of activities beginning with the agreed arrival time through the time the visit is to be completed. The schedule should include time for an opening, daily wrap-up, and closing meeting. It should also indicate when a tour of the manufacturing, quality control, and warehouse facilities will be taken.
 - e. **Audit Team members:** List the names of the auditors who are assigned to audit the facility.
2. The Lead Auditor provides the audit plan to the site representative and confirms the audit dates. The Lead Auditor discusses with the site representative safety issues that the auditors should be aware of prior to their visit.
3. A Pre-Audit Meeting is conducted upon entry into the facility. The site should have been informed of the intent for the meeting and the meeting content so that the site can have appropriate personnel present. The Pre-Audit Meeting is led by the Lead Auditor and should review the following items:
 - a. Identify the audit host and escorts for each area to be visited.
 - b. Discuss safety measures
 - c. Discuss audit schedule
 - d. Review audit purpose and scope
 - e. Confirm lunch arrangements
 - f. Establish timing of a daily meeting and audit closing meeting
 - g. Review audit findings, ratings, and possible audit outcomes

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- h. Discuss post-audit activities including report preparation, site review of the draft report including the rating of findings, site addendum of corrective measures to the report, and responsibility for follow-up of the corrective measures.
 - i. Auditor request to see selected procedures.
4. It is advisable to begin the audit with a review of the site process flow diagram so as to identify those manufacturing areas where a visit is most appropriate. Such areas involve operations that can have an impact on excipient quality such as manufacturing, packaging, and bulk storage. It is also advisable to identify that point in the manufacturing process where the site has determined excipient GMP principles should be applied.
5. Once the Pre-Audit Meeting has been conducted, the flow diagram has been reviewed, and the schedule for visiting the various areas of the facility has been established, the inspection commences. Note that the auditor must report to IPEA Executive Management any activity or situation that presents a significant risk to consumers or significantly compromises good manufacturing practices at the facility.
6. The auditor is escorted in the facility by the site host and/or the area escort. During the tour of the facility, it is important that the auditor:
 - Stay with the host and/or area escort.
 - Not touch any equipment, devices, containers, etc. unless deemed necessary and permission has been granted by either the escort or area representative.
 - Take detailed notes of the observations made during the inspection.
 - Be observant. Record both positive and negative observations.
 - Listen carefully to the answers provided by the site personnel interviewed.
7. The audit includes a detailed examination of all operational activities related to manufacturing, packaging and labeling, testing, bulk storage, sampling, and warehousing of the excipient with emphasis on:
 - a. Operational areas with focus on process steps that are open to environmental contamination particularly where subsequent steps do not purify the excipient.
 - b. Operations that purport to remove contaminants such as washing, filtering, or the use of magnets.
 - c. Water quality where the excipient may be affected by the quality of the water.
 - d. In-process and finished product sampling and sampling devices with an emphasis on their appropriateness and proper cleaning and storage.
 - e. Packaging and labeling to assure efforts to prevent the risk of mix-up are adequate.
8. The site visit includes a review of various site procedures. It is important to request procedures during the Pre-Audit Meeting that convey an understanding of the operation of the site GMP Quality System such as those noted below. Upon

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completion of the visit to the various areas of the plant, the balance of the time remaining for the site audit should be spent reviewing SOPs, Work Instructions, and records. Procedures and records of particular interest include but are not limited to:

- a. Change Control and notification of significant change,
 - b. Training, including GMP,
 - c. Good documentation practices,
 - d. Batch records
 - e. Test records,
 - f. Out-of-specification and out-of-trend issues
 - g. Quality release,
 - h. Retain sample,
 - i. Stability program,
 - j. Manufacturing Instructions,
 - k. Equipment Use Logs, and
 - l. Internal audit
 - m. Equipment, Process & Cleaning Qualification and Validation
 - n. Complaint handling and investigations
9. Lunch arrangements are made by the host. It is preferable to have lunch brought to the site rather than go to a restaurant. Since the duration of the audit is limited, it is important to spend as much time conducting the audit as is practical.
10. The site determines the attendance at the Closing Meeting. However, it is advisable to encourage the facility to have the senior site employee in attendance, as well as representatives from the various operations visited. This assures these key personnel have an opportunity to hear the audit observations and tentative ratings and to respond while the auditor is on-site. This facilitates the preparation of an audit report that is factually correct, with no adverse observations that the site has not already been made aware of, that will be in the report.

In conducting the Closing Meeting, it is advisable to begin with positive observations that can be made about the facility. It is important to have prepared for the meeting a draft of the adverse observations that the facility might want to review and discuss. Since at the Closing Meeting the observations are a first draft, it is advisable to have the site individuals take notes. However, a copy of the draft observations can be given to the site at the discretion of the auditor.

11. As noted in SOP 24, any potentially adverse observations should be reported with a statement of the observation, with no embellishment, followed by a statement of the supporting documentation or visual observation where appropriate and concluding with the observation's rating. For example, if an individual is found not to be following Good Documentation Practices, it would be reported as an observation of the deficient activity including the identity of the specific record where this observation was made and the rating.

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12. During an audit, it is possible that a difference of opinion can arise as to the severity of an observation. It is important not to spend too much time debating the merits of the observation. If it does not appear that the difference of opinion can be resolved, then the auditee should be informed that the audit report is subject to review by both representatives of IPEA and the site and that the matter can be resolved during the review process.
13. Where a Surveillance Audit is conducted to verify that the site continues to be in substantial conformance to excipient GMP expectations, the audit is conducted in the same manner as the Certification Audit except the Surveillance Audit:
 - a. Begins with a review of the findings from the previous audit to confirm that the corrective or preventive measures the site committed to implement were completed according to the schedule. The audit also verifies that those measures that were completed are effective.
 - b. Reviews changes made at the site or above site that may affect the performance of the site quality system.
 - c. Examines those activities that were designated in the audit plan.
 - d. Assesses those areas not already audited.
14. At the completion of the visit it is important to remind the host that the site will receive a copy of the audit report for their review and comment prior to submission to the Certification Board.
15. IPEA sends a copy of the draft audit report to the applicant.
16. The applicant reviews the report and notifies IPEA of any editorial or factual errors. The applicant returns the draft report within 2 weeks unless an extension has been requested and granted by IPEA Executive Management.
17. IPEA Executive Management discusses any factual change requests with the Lead Auditor and the report is modified accordingly. All changes to the draft report are to be made in the same file that was sent to the site for review.
18. IPEA issues the final audit report and provides it to the Certification Board for their review and consideration in accordance with SOP 8.

HISTORY OF REVISIONS

Revision No.	Effective Date	Description of Changes
0	Mar. 13, 2009	New Procedure
1	Dec. 7, 2010	Changed references from SOP 5 to SOP 24 and added clarity
2	Aug. 18, 2011	Update Flow Diagram to reflect SOP 14