

STANDARD OPERATING PROCEDURE
International Pharmaceutical Excipients Auditing, Inc.

Title Documenting the Certification Audit		Revision 1	SOP Number 24
Originator Irwin Silverstein	Approved By IPEA Management Committee	Effective Date Feb 17, 2011	Page Page 1 of 17

PURPOSE:

This procedure establishes documentation expectations for Certification Audit reports.

SCOPE:

This procedure applies to all audits that are performed for IPEA for Excipient GMP Conformance Certification.

RESPONSIBILITIES:

1. **Lead Auditor:** responsible for issuing a draft report whose contents are in conformance with this procedure.
2. **Qualified Auditor:** responsible for supporting the Lead Auditor in the conduct of the audit.
3. **Report Reviewer:** responsible for confirming that the contents of the report conform to this procedure.

REFERENCES:

1. SOP 9, Certificate of Excipient GMP Conformance
2. SOP 20, Conducting the Certification Audit.

DEFINITIONS:

1. See Glossary

PROCEDURE:

I. On-site Documentation

A. General Guideline

- i. Audits are to be conducted using the current IPEC Good Manufacturing Practices Audit Guideline. Documentation of the audit can be done using Appendix B or any other means where reference is made to the audit items listed in the Audit guide.
- ii. The Lead Auditor is responsible for assuring that the audit is conducted in accordance with the audit plan (see SOP 20).
- iii. The auditor documents all observations made at the site. Wherever possible, the observations recorded should contain sufficient detail so that an individual would be able to make the same observation if so desired (I.A.iii.a). Exceptions to this are instances where the observation is of a visual nature and not one of document review (I.A.iii.b).
 - a. Where the observation concerns a written record or other document, the item should be uniquely identified so that it is possible to retrieve the same document.
 - b. Where the observation is visual in nature, then the circumstances should be recorded such as the location and date and time.
- iv. Where multiple instances of related findings are noted, the audit report summarizes the scope of the problem so that a reader can evaluate the severity, e.g. 3 of 5 batches with documentation errors.

B. Certification Audit

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- i. This initial visit to the facility or a visit where over 3 years has elapsed emphasizes documenting the GMP quality system. The site visit evaluates the quality system to assure the excipient is produced in conformance to GMP requirements. 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 is in contact with 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.
 - ii. The site visit includes a review of various site procedures. Procedures and records of particular interest are listed but not limited to:
 - a. Change Control and notification of significant change,
 - b. Training, including GMP,
 - c. Good documentation practices,
 - d. Test records,
 - e. Quality release,
 - f. Retain sample,
 - g. Stability program,
 - h. Manufacturing Instructions,
 - i. Equipment Use Logs, and
 - j. Internal audit
- C. Surveillance Audit
- i. 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.

II. Draft Audit Report

- A. Audit observations should be statements of fact and should be accurate. Observations should be brief and to the point.

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- i. Observations should ordinarily describe who, what, and where. They should be specific and identify precise situations and facts.
- ii. The use of “Why” should be avoided unless absolutely necessary to enhance the meaning and should be support with facts.
- iii. Observations should not draw conclusions as to conformance or non-conformance.
- iv. The term “compliance” should never be used in a report as it has a legal interpretation. Avoid using words that draw conclusions such as “safe” or “unsafe”.
- v. Universal statements are inappropriate since the audit is generally only a sampling of the sample population and not a comprehensive review of every item.
- vi. The report should avoid inclusion of proprietary or confidential information unless reference is essential to the observation.
- vii. Acronyms should be defined at the first use in the report.

III. Final Audit Report

- A. The audit report consists of two parts; a front portion comprised of summary information including company and site details, list of auditors, auditor qualifications, and the executive summary; and the site observations. The contents and format of the front part is established in Appendix A. Many of the items in part 2, Audit Information, and section 3, Supplier Profile, can be obtained from the pre-audit questionnaire (See SOP 3).
 - i. Part 1, Executive Summary, should indicate the essential findings of the audit. The summary should note the excipient covered by the report, the processing step where the site has established full GMP requirements begin, and a statement of the guideline and monograph used. The summary should also include noteworthy positive aspects to the visit such as cooperation of staff, housekeeping and maintenance, etc.
 - ii. The Executive Summary should list significant observations that cause concern for conformance to GMP requirements. The observation should be a statement of fact without drawing conclusions. It should include the guideline number under which a reader can find additional details, including the GMP requirement statement. These observations are intended to alert the site that there is an opportunity for improvement to the quality system. Items that are rated Substantially Meets are not included in the Executive Summary.
- B. The audit report is documented using the IPEA Audit Report Template, Appendix B. The observations should be entered into the column labeled “Notes” in the appropriate row. Where the observation indicates the need or an opportunity for improvement, the text is presented in bold typeface. If a guideline requirement is not appropriate for the site, indicate in the notes column either N/A or not applicable.
- C. There should be a separate audit report for each excipient audited at the site. Where multiple grades of the excipient are produced using the same materials, equipment, and personnel, a single report is to be issued. Where the excipient is also produced in another facility or site, separate reports for each site are to be issued.

IV. Rating Observations

- A. There are six Auditor judgments used for summarizing the various Sections to the

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checklist:

Fully Meets (FM)	Meets or exceeds the intent of the checklist in design and execution.	Evidence indicates system is effective. An effective, well-developed and executed Quality System. All checklist criteria for the section have been addressed, as applicable to this facility's programs. Procedures are established, maintained and documented where so noted in the checklist, and can be corroborated by multiple parties and verified by objective evidence.
Substantially Meets (SM)	Most of the elements established by the GMP Audit Checklist were in place . (Almost "Fully Meets")	Evidence indicates a good, functional Quality System is in place. However, 1) a few applicable, minor audit checklist elements are not followed, 2) minor inconsistencies exist between implementation versus documented procedure, 3) minor examples are evident of flawed record keeping, and / or 4) informal practices cannot be corroborated by multiple parties or objective evidence. (The term "minor" as used in this definition means that the observation is one that, if left uncorrected, could not adversely impact product quality, safety or security.) A corrective action plan is provided at the discretion of the Applicant.
Partially Meets (PM)	Most of the elements established by the GMP Audit Checklist were not in place (Almost a "Does Not Meet")	Evidence indicates a semi-functional Quality System is in place. However, 1) most applicable, minor audit checklist elements are not followed in that section, 2) implementation has little resemblance to documented procedure, and / or 3) record keeping is misleading, inaccurate or nonexistent. (The term "minor" as used in this definition means that the observation is one that, if left uncorrected, could not adversely impact product quality, safety or security.) The Applicant must submit a corrective action plan.
Does Not	Key system	Evidence indicates Quality System is not

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Meet (DM)	elements of checklist missing and / or poorly designed and / or poorly executed.	effectively developed or implemented. System is poorly designed or not followed. Multiple applicable checklist criteria for the section are missing or not performed. Multiple or repetitive deviations observed in execution or key records. The Applicant must submit a corrective action plan.
Critical Failure (CF)	Clear evidence or direct observation that adulterated product might be released and / or a clear regulatory failure .	Critical violation of GMPs with practices or conditions leading to confirmed or highly probable adulteration of product, or significant deficiencies in required regulatory programs, likely to result in product recall or facility closure; and deficiencies likely would have gone undetected in the absence of the auditor.
Not Applicable or Not Auditable (NA)	A system that is not needed or major portions are not controlled at this facility.	Systems described in this section are not needed because of the nature of products or processes at this facility, or systems are controlled somewhere other than by the facility, e.g., corporate, and there is insufficient direct evidence for the auditor to verify actual practices of the key criteria in the section or judge their consistency or effectiveness.

HISTORY OF REVISIONS

Revision No.	Effective Date	Description of Changes
0	Mar 13, 2009	New procedure
1	Feb 17, 2011	Minor revisions and added requirement for corrective action where item rated DM or PM

**INTERNATIONAL PHARMACEUTICAL EXCIPIENTS
AUDITING, INC.**

***Excipient GMP Conformance Certification
Audit Report***

[Application Number]
[Company Name]
[Facility Address]
[Excipient Compendial Name]

Dates of Audit:

Date of Report:

I believe this report accurately describes the observations made during the audit.

Signed (lead auditor):

Lead auditor (typed name):

1. EXECUTIVE SUMMARY

[Insert an overall impression of the facility and staff.]

The following observations were noted and suggested for possible improvement. These as well as other less significant observations and opportunities for improvement are detailed in the body of the report and identified by **bold type** in the audit details section.

- [List all significant improvement opportunities plus the section number]

2. AUDIT INFORMATION

Supplier's name	
Supplier's mailing address	
Address of audited location	
Primary supplier contact	
Telephone	
Fax	
e-mail	
Audit guideline used	The IPEC-PQG Good Manufacturing Practices Guide For Pharmaceutical Excipients
Version of audit guideline	2007

- 2.1 **Purpose of Audit:** The determination of adherence to IPEC recommended GMP practices at the [Company name and address] site in the manufacture of Excipient NF.
- 2.2 **Scope of Audit:** Site inspection included review of the Quality Management System and the [list site operations assessed].

3. LIST OF ATTACHMENTS

- Attachment 1 [Organization Chart]
Attachment 2 [Process Flow Diagram]

PERSONNEL PARTICIPATING IN THE AUDIT

AUDIT TEAM MEMBERS

Lead Auditor

NAME	TITLE	ORGANIZATION/ADDRESS

Associate Auditor(s)

NAME	TITLE	ORGANIZATION/ADDRESS

SUPPLIER PERSONNEL

NAME	TITLE	DEPARTMENT

AUDITOR(S) QUALIFICATIONS

[Summarize the qualifications of the Lead Auditor and any Qualified Auditor(s) for conducting this audit.]

SUPPLIER PROFILE

Number of Employees in the Company:	
Number of Employees at Site:	
Language Spoken:	
Language Written:	
Types of Products Made:	
Excipient Compendia or Chemical Name:	
Excipient Trade Name:	
Excipient Manufactured under ISO 9001 Certification:	
ISO Certifying Authority:	
Quality Policy:	
Other Certifications:	
Date of Last Inspection by Regulatory Agency:	
Name of Agency:	
Date of Last Recall:	
Other Operations or Subcontractors:	
List Other Operations or Subcontractors:	
US Drug Master File Number (Yes or No):	
Batch or Continuous Process plus Definition:	
Description of Lot Numbering System:	

IPEA Certification Audit Report Template

GMP SECTION	ITEM	COMMENTS	Rating
4 QUALITY MANAGEMENT SYSTEMS-EXCIPIENT QUALITY SYSTEMS			
4.1 General Requirements			
4.2 Documentation Requirements			
4.2.1 General			
4.2.2 Quality Manual	<ul style="list-style-type: none"> • Quality Manual • Quality Policy • GMP starting point 		
4.2.3 Control of Documents	<ul style="list-style-type: none"> • Written manufacturing instructions • Process fully described • Verification of significant steps • SOP availability and control • Periodic review of SOPs • Electronic control 		
4.2.4 Control of Records	<ul style="list-style-type: none"> • Record retention SOP • Good Documentation Practices 		
4.3 Change Control	<ul style="list-style-type: none"> • Change control procedure • Control of production changes • Independent approval of changes • Impact on qualification or validation • Change control log • Notification to customers & regulatory 		
5. MANAGEMENT RESPONSIBILITY			
5.1 Management Commitment	<ul style="list-style-type: none"> • Commitment to customer satisfaction • Commitment to GMP compliance 		
5.2 Customer Focus	<ul style="list-style-type: none"> • Customer requirements • Customer audit policy 		
5.3 Quality Policy	<ul style="list-style-type: none"> • Policy deployment, management support • Continual improvement 		
5.4 Planning	<ul style="list-style-type: none"> • Measurable conformance objectives 		
5.4.1 Quality Objectives	<ul style="list-style-type: none"> • Conformance objectives 		
5.4.2 Quality Measurement System Planning	<ul style="list-style-type: none"> • Adequate resources 		
5.5 Responsibility, Authority and Communication			

GMP SECTION	ITEM	COMMENTS	Rating
5.5.1 Responsibility and Authority	<ul style="list-style-type: none"> • Reporting relationship of Quality Unit and Production (organization charts) • Job descriptions • Clarity of Quality Unit authority and responsibilities, delegation • Batch release 		
5.5.2 Management Representative	<ul style="list-style-type: none"> • Periodic conformance reports to top management 		
5.5.3 Internal Communication	<ul style="list-style-type: none"> • Quality system communication • Top management notification of quality critical issues 		
5.6 Management Review			
5.6.1 General	<ul style="list-style-type: none"> • Senior management quality system review 		
5.6.2 Review Input	<ul style="list-style-type: none"> • Defined 		
5.6.3 Review Output	<ul style="list-style-type: none"> • Resources and improvements identified 		
6. RESOURCE MANAGEMENT			
6.1 Provision of Resources	<ul style="list-style-type: none"> • Adequate resources 		
6.2 Human Resources			
6.2.1 General	<ul style="list-style-type: none"> • Education, training, experience • Consultant qualifications 		
6.2.2 Competence, Awareness and Training	<ul style="list-style-type: none"> • Adequate training, experience, and qualifications • Training SOP • Training program • Trainer qualifications • GMP training records • GMP training frequency • Measure of training effectiveness • Communicating changing regulations 		
6.2.3 Personnel Hygiene	<ul style="list-style-type: none"> • Personal hygiene training • Clothing • Reporting of illness • Loose items like jewelry and pens • Consumption of food, beverage, and tobacco products • Access control 		

GMP SECTION	ITEM	COMMENTS	Rating
6.3 Infrastructure (Facilities and Equipment)			
6.3.1 Building and Facilities	<ul style="list-style-type: none"> • Space • Contamination control • Toxic products • Environmental controls • Laboratory facilities • State of repair 		
6.3.2 Equipment	<ul style="list-style-type: none"> • Commissioning • Maintenance • Outdoor equipment 		
6.3.2.1 Equipment Construction	<ul style="list-style-type: none"> • Contact surfaces • Lubricants, coolants, etc. • Design to minimize contamination 		
6.3.2.2 Equipment Maintenance	<ul style="list-style-type: none"> • Procedures • Records • Hand over/hand back 		
6.3.2.3 Computer Systems	<ul style="list-style-type: none"> • Access controls • Change controls • Consistent function • Back up, disaster recovery 		
6.3.3 Utilities	<ul style="list-style-type: none"> • Risk of contamination 		
6.3.4 Water	<ul style="list-style-type: none"> • Specification • Treatment and monitoring • Positive pressure/back flow 		
6.4 Work Environment			
6.4.1 Air Handling	<ul style="list-style-type: none"> • Effectiveness • Recirculation 		
6.4.2 Controlled Environment	<ul style="list-style-type: none"> • Required • Monitoring • Deviations 		
6.4.3 Cleaning and Sanitary Conditions	<ul style="list-style-type: none"> • Appropriately clean • Procedures, schedules • Waste control 		
6.4.4 Pest Control	<ul style="list-style-type: none"> • Free of infestation • Contractor controls • Records, review of effectiveness 		
6.4.5 Lighting	<ul style="list-style-type: none"> • Adequate 		

GMP SECTION	ITEM	COMMENTS	Rating
6.4.6 Drainage	<ul style="list-style-type: none"> • Adequate • Air break 		
6.4.7 Washing and Toilet Facilities	<ul style="list-style-type: none"> • Adequate facilities • Clean 		
7. <u>PRODUCT REALIZATION</u>			
7.1 Planning of Product Realization	<ul style="list-style-type: none"> • Process flow diagram • Critical parameters • Batch or continuous • Multi purpose • Equipment & lines ID 		
7.2 Customer-related Processes			
7.2.1 Determination of Requirements Related to the Product	<ul style="list-style-type: none"> • Customer requirements • Agreed additional requirements 		
7.2.2 Review of Requirements Related to the Product	<ul style="list-style-type: none"> • Mutually agreed specifications • Contract review 		
7.2.3 Customer Communication	<ul style="list-style-type: none"> • Implementation of customer requirements • Notification to customers of significant changes 		
7.3 Design and Development	<ul style="list-style-type: none"> • Technology transfer 		
7.4 Purchasing			
7.4.1 Purchasing Process	<ul style="list-style-type: none"> • Qualification and control of suppliers • Approved supplier list • Audit of key suppliers • Selection and control of subcontractors • Follow-up of audit corrective actions • Material specifications • BSE/TSE, etc. risks 		
7.4.2 Purchasing Information	<ul style="list-style-type: none"> • Purchasing agreement • Supplier review of specifications • Supplier notification of significant change 		
7.4.3 Verification of Purchased Product	<ul style="list-style-type: none"> • Procedure for approval and release • Quarantine • Sampling procedures and conditions • Testing/verification • Bulk deliveries 		

GMP SECTION	ITEM	COMMENTS	Rating
7.5 Production and Service Provision			
7.5.1 Control of Production and Service Provision			
7.5.1.1 Production Instructions and Records	<ul style="list-style-type: none"> • Controlled master batch instructions • Retrievable batch records • Suitable details 		
7.5.1.2 Equipment Cleaning	<ul style="list-style-type: none"> • Dedicated or controls for cross-contamination • Cleaning effectiveness and justification • Documentation of cleaning • Storage of utensils and sampling devices • Continuous processes, frequency of cleaning 		
7.5.1.3 Recovery of Solvents...	<ul style="list-style-type: none"> • Controls in place • Traceability 		
7.5.1.4 In-Process Blending /Mixing	<ul style="list-style-type: none"> • Blending procedures • Defined blending parameters • Part containers/tails 		
7.5.1.5 In-Process Control	<ul style="list-style-type: none"> • Program • Sampling procedures • Results recorded • Control actions 		
7.5.1.6 Packaging and Labeling	<ul style="list-style-type: none"> • Procedures • Label control • Mix-up prevention 		
7.5.1.7 Records of Equipment Use	<ul style="list-style-type: none"> • Sequence of activities 		
7.5.2 Validation of Processes for Production and Service Provision	<ul style="list-style-type: none"> • Process consistency 		
7.5.3 Identification and Traceability			

GMP SECTION	ITEM	COMMENTS	Rating
7.5.3.1 Traceability	<ul style="list-style-type: none"> • Material to their manufacturer • Material through production • Unique batch numbering • Batch definition for continuous processing • Traceability of reprocessed material • Origin of manufacturing site 		
7.5.3.2 Inspection & Test Status	<ul style="list-style-type: none"> • Approval of materials & packaging • Controls for unapproved materials • Identification of containers and equipment • Status identification • Identification of unlabeled container • Evaluation of raw materials beyond expiration or use date • Quarantine control 		
7.5.3.3 Labeling	<ul style="list-style-type: none"> • Excipient labeling content • Special storage condition labeling 		
7.5.4 Customer Property	<ul style="list-style-type: none"> • Procedures • Agreements for confidential information 		
7.5.5 Preservation of Product			
7.5.5.1 Handling, Storage, and Preservation	<ul style="list-style-type: none"> • Appropriate conditions and record • Outdoor storage • Bulk storage dispensing • Stock rotation 		
7.5.5.2 Packaging Systems	<ul style="list-style-type: none"> • Adequate protection to excipient • Storage of packaging components • Reusable packaging • Bulk container cleanliness • Bulk container seals • Tamper evident seals 		
7.5.5.3 Delivery and Distribution	<ul style="list-style-type: none"> • Distribution records • Traceable to consignee • Retrieval or market withdrawal procedure 		

GMP SECTION	ITEM	COMMENTS	Rating
7.6 Control of Measuring and Monitoring Devices	<ul style="list-style-type: none"> • Calibration procedures, records, and status • Standards-handling and storage • Frequency and limits • Out-of-calibration actions 		
8. MEASUREMENT, ANALYSIS AND IMPROVEMENT			
8.1 General	<ul style="list-style-type: none"> • Quality management processes 		
8.2 Measurement and Monitoring			
8.2.1 Customer Satisfaction	<ul style="list-style-type: none"> • Measurements (e.g. complaints, returns, feedback) 		
8.2.2 Internal Audit	<ul style="list-style-type: none"> • Program, conducted; frequency • Audit documentation • Corrective measures • Verification of corrective actions 		
8.2.3 Measurement and Monitoring of Processes	<ul style="list-style-type: none"> • Measurement of critical process control points • Use of appropriate techniques • Periodic review and actions 		
8.2.4 Measurement and Monitoring of Product	<ul style="list-style-type: none"> • Documented test methods • Fit for purpose • Compendial methods used • Compendia changes • Periodic reviews of product quality 		
8.2.4.1 Laboratory Controls	<ul style="list-style-type: none"> • Procedures and recorReagent and standards 		
8.2.4.2 Finished Excipient Testing & Release	<ul style="list-style-type: none"> • Quality Unit responsibility • Testing instructions • Release criteria • Continuous processes 		
8.2.4.3 Out-of-Specification Test Results	<ul style="list-style-type: none"> • Procedures, records and actions 		
8.2.4.4 Retained Sample	<ul style="list-style-type: none"> • Kept, size, and storage • Retention period 		
8.2.4.5 Certificates of Analysis	<ul style="list-style-type: none"> • Format and content • Alignment to specification • Skip lot testing 		
8.2.4.8 Impurities	<ul style="list-style-type: none"> • Defined and controlled • Residual solvents 		

GMP SECTION	ITEM	COMMENTS	Rating
8.2.4.7 Stability	<ul style="list-style-type: none"> • Data to support storage conditions • Determination of expiry/re-evaluation period • Stability program • Container type • Stability indicating method and parameters • Results review and actions 		
8.2.4.8 Expiry/Retest periods	<ul style="list-style-type: none"> • Defined and communicated 		
8.3 Control of Nonconforming Product	<ul style="list-style-type: none"> • Procedure and records • Process to retrieval • Quarantine • Destruction records 		
8.3.1 Reprocessing	<ul style="list-style-type: none"> • Reprocessing instructions 		
8.3.2 Reworking	<ul style="list-style-type: none"> • Rework instructions • Excipient quality impact assessment 		
8.3.3 Returned Excipient Product	<ul style="list-style-type: none"> • Procedures and records • Identified and quarantined 		
8.4 Analysis of Data	<ul style="list-style-type: none"> • Measures of Quality Management System effectiveness • Types of data • Periodic reviews 		
8.5 Improvement			
8.5.1 Continual Improvement	<ul style="list-style-type: none"> • Inputs that identify continual improvement opportunities 		
8.5.2 Corrective Action	<ul style="list-style-type: none"> • Root cause analysis • Complaints 		
8.5.3 Preventive Action	<ul style="list-style-type: none"> • Risk assessment 		