

Auditing an Active API Manufacturer

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Audit Training Manual: 017

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is evaluated in terms of whether it does or does not exist, with respect to a given requirement.

Crystallization: The formation of pure to nearly pure crystals of small or big molecules. Often used to purify a substance; crystallization of proteins is used to obtain their three-dimensional structure by x-ray analysis.

Deviation: Departure from an approved instruction or established standard.

Distillation: A process in which liquid is boiled, vaporized and condensed to increase purity.

Endotoxin test: A test designed to determine if there are endotoxins in the API/drug product. Endotoxins are toxic molecules consisting of lipopolysaccharide originating from the outer cell wall of Gram-negative bacteria. Endotoxins may cause a fever reaction in humans.

Expected yield: The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale or manufacturing data.

Extraction: The removal of a chemical from a mixture by the use of a selective solvent.

Fermentation: A process in which an agent such as yeast, a bacterium, mold or enzyme causes an organic substance to break down into simpler substances.

Filtration: The separation of a solid from a fluid by passing the liquid through a filter, cloth, or other porous medium.

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Heel: An expression used for build-up of material in equipment used for continuous or campaign production leading to a risk of carry-over of contaminants (e.g. impurities or microorganisms). Examples of risks for significant carry-over between batches are filtration and micronisation.

Impurity: Any component present in the intermediate or API that is not the desired entity.

Impurity profile: A description of the identified and unidentified impurities present in an API.

Master production instruction: The approved process document or “recipe” that is used for preparing every batch of the intermediate and API.

Mother liquor: The residual liquid that remains after the crystallization or isolation processes. A mother liquor may contain materials that did not react, intermediates, levels of the API, and/or impurities. It can be used for further processing.

Parenteral: A pharmaceutical term used to describe a drug product that is sterile and delivered through injection/infusion.

Pyrogen: A substance that can produce a fever in an animal system.

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increases throughout the production process from starting materials through intermediates to API and it is important for the manufacturer to define where GMP starts. Table 1 in Q7A gives guidance in application of GMP.

In a cell culture/fermentation process, Q7A applies to the following:

- Maintaining the working cell bank
- Cell culture and/or fermentation
- Isolation and fermentation
- Physical processing and packaging

GMP is to be applied to the manufacture of APIs for use in Medicinal Products. If the API is to be used to manufacturing a non-sterile Medicinal Product, Q7A applies to the following:

- Introduction of API starting material
- Production of intermediates
- Isolation and purification
- Physical processing and packaging

If the API is to be used in a manufacturing process for a sterile product but does not need to be sterile in itself additional requirements need to be considered such as quality of water used and type of facilities used for the final steps

If the API is required to be sterile to be used in an aseptic manufacturing process, this training module will only cover the API process up to the point where the product is becoming sterile (e.g. filtration with a sterilizing filter).

GMPs should increase in the level of sophistication and documentation as an API process nears production of the final API. This includes more detail in batch record, level of sophistication of analytical methodology, and level of protection from contamination with more stringent environmental controls.

What is an API audit?

An API audit is an audit of the buyer site to the suppliers.

The goal of an API audit should be to verify that the sites comply with the principles of GMP for APIs. In order to certify/qualify deliveries the manufacturing and testing facilities used by the manufacturer need to be audited in order to evaluate possibilities for accepting material based on Certificates of Analyses rather than performing full in-house testing. API audits are part of the certification program and should be performed regularly according to an approved schedule.

Providing high quality chemicals to pharmaceutical dosage form manufacturers is of critical importance in safeguarding the health and well being of our patients. This training unit will outline the requirements and steps to follow in the performance of QA Audits of API processing operations. To see how GMP is applied, it is important to understand the API process.

General Overview of API Manufacturing

Manufacturing process for Chemical APIs

The chemical synthesis process begins when raw materials and solvents are brought together and charged into vessels (reactors) with a subsequent chemical reaction. Typical

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- Intermediates for use outside the control of the manufacturing company,
- Raw materials,
- Packaging materials, and Labels.

In addition they need to review completed production and lab records of critical process steps and perform product quality reviews.

The Quality Unit must also approve specifications and master production instructions, all procedures impacting on quality, contract manufacturers, changes that potentially impact quality, and validation protocols and reports. The Quality Unit also has the responsibility to ensure that:

- Critical deviations are investigated
- Internal audits are performed
- Process changes are evaluated and approved
- Facilities are maintained in a good state of repair
- Effective systems exist for qualification, calibration, control and maintenance of critical equipment
- Utilities (e.g. water, compressed gases) are qualified and monitored
- Effective systems exist for calibration of critical equipment
- Materials are properly controlled per their status, tested and results reported
- Product release. Note that regulations do not require a QP release of APIs.
- Annual product quality reviews are performed
- Stability data exists to support retest or expiration periods
- Rework/reprocessing is controlled

Personnel

Qualified personnel must be available to perform and supervise the manufacture, processing, packing, holding, and testing of APIs.

A special dress code should be in place for controlled areas. The site should have a written approved SOP describing the dress code.

Buildings and Facilities

Buildings and facilities must be of suitable size, construction, environment, and designed to minimize contamination and cross-contamination of APIs.

ICH Q7A requires dedicated production areas for production of highly sensitizing material such as penicillins or cephalosporins. This should include separate air handling systems for the isolation and packaging of these materials. Constructions that ensure containment are beneficial with regards to minimizing cross contamination/contamination risks.

Furthermore ICH Q7A says that 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 cytotoxics unless validated inactivation and/or cleaning procedures are established and maintained. The current position of many sites is that penicillins must be produced in dedicated facilities. For the other products a risk assessment of the potential for cross contamination from multi product facilities should be undertaken, taking into account factors such as the potency, cleanability, containment technology and facilities / equipment used.

Many API plants are predominantly closed systems and focus should be given to points of materials addition, or product removal / isolation, when the system is open to the environment.

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A new accommodation of a product into an existing plant should take account of the attributes of the product and the capability and design of the plant with respect to cleaning.

Performance of cleaning processes must be documented. Status of cleaning and maintenance should be recorded and checked, (e.g. a logbook or cleaning record). The need for cleaning should also be considered for transfer of APIs or intermediates between reactors.

Documentation and Records

Any production, control or distribution record specifically associated with a batch of API should be retained as required by the regulations. These documents may be retained in paper or electronic form. Written procedures should be established and followed for investigating unexplained discrepancies and include results out of the expected yield range, batch failure to meet specification and out of specification results. An annual product quality review should be performed on a representative number of batches and their associated records, which include process changes, stability data, complaints, recalls, returned APIs and deviation investigations.

Materials Management

The criticality of each raw material to the API process and its key quality attributes must be understood and factored into the controls applied to it. Raw materials should only be sourced from formally approved suppliers. This should include an evaluation, which provides adequate evidence that the manufacturer can consistently provide product meeting all specification clauses. As a minimum one test should be completed on receipt to confirm the identity of the material. Full analytical testing of receipted materials can be reduced once confidence in a supplier has been established but only after a minimum of three separate conforming batches/deliveries have been received and tested.

Raw materials (including those received in tank trucks) and packaging materials should be received, sampled, tested, approved and stored.

Materials received in tank trucks should also be quarantined, tested and released prior to loading them into the tank farm. Non-dedicated tankers should be accompanied by a cleaning certificate for each supply. Large storage tanks or silos in the tank farm should be identified and their contents periodically tested to assure no deterioration occurs.

Packaging and labeling materials should also be sampled, tested, and released for use based on established specifications. Labels should be stored in a secure location, with limited access. Printed labels should be reconciled.

Validation and Production Controls

For API processes, validation is required for critical steps, which need to be defined during development. The steps of the synthesis requiring formal validation should be identified. Validation should ensure that the manufacturing process has the capability to produce a consistent product in a reliable manner. Validation should include API steps that are critical to the quality and purity of the final API product.

Process validation defines the API in terms of Critical Quality Attributes.

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It is the responsibility on the manufacturer to ensure that the shipping contractor knows and follows appropriate conditions.

Laboratory Controls

GMP requirements for API laboratories are the same as the laboratory requirements for finished dose drug products.

Laboratory reagent "use by" dates should be determined using experience and sound scientific judgment and do not require formal stability programs.

The impurity profile of an API should be compared, at appropriate intervals, to the profiles submitted in the regulatory submission or to historical data to detect changes resulting from modifications in raw materials, equipment operating parameters or the production process.

The degree of validation of analytical methods should reflect the purpose of the analysis and the stage of the API process. Validation of methods may not be required for raw materials, solvents, packaging materials. Validation is required for APIs and critical intermediates. The degree of validation of in-process methods depends on the criticality and purpose of the test.

Appropriately identified reserve samples of each API batch should be retained for at least one (1) year after the expiry date of the batch assigned by the manufacturer, or for three (3) years after distribution of the batch, whichever is longer. The reserve samples should be stored in the same packaging system in which the API is stored. Sufficient quantities should be retained to permit analyzing should the need arise.

Certificate of Analysis

The certificate of analysis should contain information about the API or intermediate as shown below. The Certificate of Analysis should be complete, signed and dated by a Quality Unit representative.

Certificate of Analysis for an API or Intermediate		
Name of API or intermediate:		
Grade (if appropriate):		
Date of Manufacture:		
Date of Release:		
Expiration Date (if applicable):		
Retest Date (if applicable):		
Compendial or customer requirements testing performed:		
Type of Test	Requirement (acceptance limits)	Result (actual numerical result if test result is numerical)
Authorized by: _____ (Quality Unit) Name of manufacturer: Address: Telephone number:		

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- Blending small batches to increase batch size
- Blending of tailings (i.e. relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch

All blending processes should be adequately controlled and documented. Each blended batch should be tested for conformance to established specifications. The batch record should include enough information to be able to trace back to the individual batches used in the blending.

If APIs are intended for use in solid oral dose forms or suspensions where physical attributes are critical, the blending operations should be validated to show the homogeneity of the combined batch. Critical attributes (e.g. particle size, distribution, bulk density and tap density) should be tested during validation since they may be affected by the blending process.

It needs to be demonstrated that there is no unacceptable build-up of impurities or microbial contamination during continuous or campaign production due to residuals left between batches/lots (heels). This includes considerations of cleaning regimes, minimizing the amount being carried over, stability to repeat operations as well as batch dating.

The risk of carry-over of contaminants can be controlled through established cleaning intervals. Examples of risks where significant carry-over can occur between batches are filtration and micronisation.

Certificates of Suitability

Manufacturers of APIs may be holders of certificates of suitability issued by the European Directorate for the Quality of Medicines, EDQM. Under this official procedure, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate concerning: the evaluation of the suitability of the monograph for the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is aimed at facilitating and simplifying exchanges between the partners to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia. Certificate including revoked certificates are listed at the EDQM website. Some but not all of the certificate holders have been inspected by EDQM.

Summary

The production of APIs must be a controlled process. As the process moves closer to producing the final API, GMPs will become more important. Depending on what the API will be used for, the level of GMP compliance will increase.

Key Parameters in Conducting an API Audit

Prior to the audit

- Determine which APIs the supplier manufactures for the site.
- Determine how the APIs will be used and in what finished drug product. If the API will be used as a direct component of a drug product, used in the preparation of a sterile drug product, or is represented by the manufacturer as being pyrogen free, this should make a difference in the audit.

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- that is endorsed by management.
- Verify that a system is in place to notify the buyer site if subcontractors are used and how subcontractors are qualified.
- Verify that a communication system is in place to notify the buyer site about 1) significant process changes prior to implementation, and 2) any stability failures that are product related.
- Ensure that quality does not delegate their responsibility and is responsible for assuring that:
 - Internal audits are performed.
 - Effective systems exist for calibration and maintenance of critical equipment.
 - Materials are tested, results reported and evaluated.
 - Stability data exists to support retest or expiration periods.
- Ensure that personnel have received adequate training.
 - Verify that there is a documented training and qualification program for each job classification.
 - Verify that job-specific training is conducted and documented for each employee.
 - Verify that training is conducted with sufficient frequency to assure that employees are familiar with current applicable regulations and are trained in process and methodology changes.
 - Verify that there are clearly written job descriptions for all personnel.
 - Confirm that all personnel comply with the dress code established for all areas of manufacturing as documented in a site SOP.
- Ensure that process equipment is controlled and qualified.
 - Verify that critical instrumentation is on a calibration and preventative maintenance program.
 - Verify that process equipment has been qualified within its operating range.
 - Verify that there is a written approved protocol/final report, which includes equipment deviations and evaluation of the deviations for impact.
 - Verify that preventative maintenance and repairs, as well as calibration operations, are documented.
- Confirm that cleaning practices are in compliance with site SOPs.
 - Determine whether equipment is dedicated to one line or process or non-dedicated. “Equipment” refers but is not limited to (utensils, sample thieves, reactors, centrifuges, tray dryer).
 - If equipment is not dedicated, ensure that it has undergone cleaning validation.
 - Assure that analytical test methods employed during cleaning validation were validated.
 - Assure that swab sampling and testing included swab recovery studies.
 - Verify that acceptable residual limits were established.
 - Ensure that there is adequate housekeeping, especially where in-process material is exposed and in the drying and packaging areas.
 - Ensure that there is an adequate system for documenting cleaning.
 - Verify that there is evidence that the cleaning process for non-dedicated equipment is adequate to remove previously manufactured material.
- Ensure that the production process is controlled and validated.
 - Verify that the process has been validated.
 - Verify that there is a procedure for clearly defining the date of manufacture.
 - Verify that there is evidence to demonstrate that the manufacturing process

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- Determine if there are any trends.
 - Determine if equipment maintenance is the root cause of process deviations.
 - Perform a review of documentation throughout the processing areas by reviewing:
 - Cleaning and use logs
 - Maintenance logs
 - Production batch records
 - Ensure that there is a complaint system in place with a means to track complaints.
 - Verify that there are complete written manufacturing instructions/batch reports that specify quantity and identity of raw materials, equipment, manufacturing flow, operating parameters, in-process sampling, packaging materials, labeling and documentation of each significant step.
 - Verify that the supplier's SOPs for cleaning and change over from one product to another have enough detail. Verify that there is adequate documentation to support the effectiveness of these procedures.
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- Ensure that there is traceability for all items included in the production of the API as well as the Finished API product.
 - Review the API stability program (stability chambers; packaging and control of samples and test data).
 - Evaluate Solvent Recovery system
 - Ensure that recovered solvent is tested against defined specifications
 - Ensure that recovered solvent is not added to a storage tank containing released solvent until all test results are received.
 - Determine that the process water used in API manufacturing is suitable for its intended use.
 - Ensure that APIs for sterile products have been produced under adequately controlled conditions
 - Verify that the manufacturing environment and equipment are adequate to minimize microbiological contamination, which includes monitoring of the environment, adequate gowning of personnel and testing of process water.
 - Ensure that computer systems have been validated.
 - Verify that computer systems have been demonstrated and documented to consistently function as expected, if used in the manufacturing process.
 - Verify that there are procedures to govern change control of computerized systems or programs, including training of personnel subsequent to changes.
 - Ensure the Quality laboratory meets GMPs standards
 - Verify that training and qualifications are documented for all laboratory personnel.
 - Verify that written and approved test methods and acceptance specifications are available to the analyst for all samples to be tested.
 - Verify that there are procedures for qualification (IQ/OQ) of new and/or modified laboratory instruments and equipment.
 - Verify that there are established practices to insure proper storage and handling of reference standards, reagents, volumetric and test solutions, with labeling to indicate their identity, date of preparation or receipt, expiration date and other appropriate information.
 - Verify that there are procedures for the preparation and maintenance of complete and appropriate written laboratory records.
 - Verify that there are procedures in place for a review of laboratory records by