Guidance for Industry

Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients

DRAFT GUIDANCE

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TABLE OF CONTENTS

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GUIDANCE FOR INDUSTRY[1]

Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients

I. INTRODUCTION

This document is intended to provide guidance on FDA's expectations regarding current good manufacturing practices (CGMP) for manufacturing, processing, packing, or holding (i.e., storage) of active pharmaceutical ingredients (APIs). Although this document focuses on the manufacture of APIs, much of the guidance provided may be useful for the manufacture of excipients. This guidance does not in any way affect the ability of the Agency to establish specific requirements or standards regarding APIs within the context of new drug application reviews. Likewise, it is not intended to address specific issues relating to the filing of such applications.

This guidance applies to the manufacture and control of drug and biologic APIs for use in human and veterinary drug products. In addition, the guidance applies to the later chemical isolation and purification steps of APIs derived from biological or fermentation processes. It also applies to sterile APIs, but only up to the point where the API is rendered sterile. The sterilization and aseptic processing of sterile APIs should be performed in accordance with CGMP regulations for finished pharmaceuticals (Title 21 Code of Federal Regulations Parts 210 & 211). This guidance also identifies CGMPs for the manufacture of APIs used in the production of drug products for clinical trials. However, it does not apply to medical gases, bulk-packaged drug products (final dosage forms), and manufacturing/control aspects specific to radiopharmaceuticals.

FDA expects appropriate CGMPs to be applied to all steps of an API manufacturing process, beginning with the use of starting materials. Such practices include the validation of processes determined to impact the quality and purity of the API. The Agency recognizes that the stringency of CGMPs in API production, such as the extent of written instructions, in-process controls, sampling, testing, monitoring and documentation, should increase as the process

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[1] This guidance has been prepared by the Division of Manufacturing and Product Quality in the Center for Drug Evaluation and Research (CDER), in a joint effort with CDER's Office of Pharmaceutical Science, the Center for Biologics Evaluation and Research (CBER) and the Center for Veterinary Medicine (CVM), in cooperation with the Office of Regional Operations (ORA). This guidance document represents the Agency's current thinking on the manufacture and control of active pharmaceutical ingredients. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For additional copies of this guidance, contact (1) the Drug Information Branch, Division of Communications Management, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-827-4573), or (2) Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Rockville, MD 20852-1448; (Fax) 888-CBERFAX or 301-827-3844 (Voice Information) 800-835-4709 or 301-827-1800.

proceeds from early steps to final synthesis and purification stages. In this guidance, the Agency attempts to clarify its expectations regarding the stringency of CGMPs at different processing steps.

APIs not manufactured in accordance with CGMPs are adulterated under Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). This section of the Act deems a drug to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMPs to ensure that such drug meets the requirements of the Act as to safety, and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

II. ORGANIZATION AND PERSONNEL

A. Responsibilities of the Quality Control Unit

There should be a quality control unit that:

- Has the responsibility and authority to approve or reject all raw materials, packaging materials, labels, and APIs;

- Has the authority to review and approve production records to ensure that no errors or deviations have occurred and, if errors or deviations have occurred, that they have been fully investigated and resolved;

- Is responsible for approving or rejecting intermediates and APIs manufactured, processed, packed, or held under contract by another company, or establishing appropriate systems to ensure that this is done by the contractor's quality control unit;

- Is one of the organizational units responsible for the review and approval of validation protocols, changes in product, process, equipment, or other changes to determine if and when revalidation is warranted;

- Has adequate laboratory facilities for the testing and approval (or rejection) of raw materials, packaging materials, and APIs;

- Is responsible for approving or rejecting all procedures, specifications, and investigations affecting the quality and purity of APIs and intermediates; and

- Is responsible for performing periodic assessments of procedures, policies, manufacturing, and control operations.

The quality control unit may delegate to the manufacturing department the responsibility and authority to perform in-process testing and release of intermediates. For example, where intermediates are not isolated and stored before use, production employees could check or test the intermediate and then immediately approve it for use in further processing.

The responsibilities and procedures applicable to the quality control unit should be in writing and followed.

B. Personnel Qualifications

Personnel engaged in the manufacture, processing, packing, holding, or testing of an API and/or intermediate should have the education, training, and experience, or any combination thereof, to enable them to perform their assigned functions. Training should extend to CGMPs as well as the particular operations employees perform. Training in CGMPs should be conducted regularly by qualified individuals and with sufficient frequency to ensure that employees remain familiar with CGMP requirements applicable to them.

An adequate number of qualified personnel should be available to perform and supervise the manufacture, processing, packing, holding, or testing of each API and/or intermediate.

C. Personnel Responsibilities

Personnel engaged in the manufacture, processing, packing, or holding of an API or intermediate should wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, should be worn as necessary to protect APIs and intermediates from contamination.

Personnel should practice good sanitation and health habits, including abstention from eating, drinking, or smoking in areas designated for production, storage, and quality control testing. Only persons authorized by supervisory personnel should enter those areas of buildings and facilities designated as limited-access areas.

Any person shown anytime (either by medical examination or supervisory observation) to have an apparent illness or open lesion that may adversely affect the safety and quality of APIs should be excluded from direct contact with raw materials, intermediates, packaging materials, or APIs until the condition is corrected or determined not to jeopardize the safety or quality of APIs. All personnel should be instructed to report any health conditions that may adversely affect APIs to supervisory personnel.

D. Consultants

Consultants advising on the manufacture, processing, packing, or holding of APIs and intermediates should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records should be maintained stating the name, address, and qualifications of any consultants and the types of service they provide.

III. BUILDINGS AND FACILITIES

A. Design and Construction Features

Buildings and facilities used in the manufacture, processing, packing, or holding of APIs or intermediates should be of suitable design, size, construction and location to facilitate cleaning, maintenance, and proper operations. Adequate space should be provided for the orderly placement of equipment and materials to prevent mixups and contamination among different raw materials, intermediates, or APIs. The flow of raw materials, intermediates, and APIs through the building or buildings should be designed to prevent mixups and contamination.

To prevent mixups and contamination, there should be defined areas and/or other control systems for the following activities:

- Receipt, identification, storage, and withholding from use of raw materials or intermediates, pending release for use in manufacturing;
- Holding rejected raw materials, intermediates, and APIs before final disposition;
- Storage of released raw materials, intermediates, and APIs;
- Manufacturing and processing operations;
- Packaging and labeling operations;
- Quarantine storage of intermediates and APIs pending release for distribution; and
- Laboratory operations.

Where microbiological specifications have been established for the API (e.g., nonsterile APIs intended for incorporation into parenteral drug products), facilities should also be designed to

limit objectionable microbiological contamination.

Operations relating to the crystallization, drying, and packaging of sensitizing APIs, such as penicillins and cephalosporins, should be performed in dedicated facilities. Dedicated facilities should also be considered for other APIs having high pharmacological activity or toxicity, such as some steroids or cytotoxic anticancer agents.

API manufacturing processes that require viral inactivation or reduction should be appropriately segregated (e.g., pre- and postviral inactivation or reduction activities).

B. Lighting

Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

C. Ventilation, Air Filtration, Air Heating and Cooling

Adequate ventilation should be provided where necessary. Equipment for the adequate control and monitoring of air pressure, microorganisms, dust, humidity, and temperature should be provided when appropriate (e.g., when APIs are exposed to the environment or handled in the final dry state).

Air filtration, dust collection, and exhaust systems should be used in production areas when appropriate. If air is recirculated to production areas, appropriate measures should be taken to control contamination and cross-contamination. Air from previral inactivation/reduction areas should not be recirculated to other areas used for the manufacture of APIs.

D. Steam, Gases, and Other Utilities

Steam that comes into contact with APIs and intermediates should be tested and monitored to ensure that it is of suitable quality and devoid of contaminants, such as boiler additives, that could adversely affect API quality.

All other utilities (e.g., gases, compressed air) that come into contact with APIs and intermediates should comply with appropriate specifications and not alter API quality beyond its established specifications.

E. Plumbing, Washing, and Toilet Facilities

Potable water should be supplied under continuous positive pressure in a plumbing system free from defects that could lead to the contamination of APIs or intermediates. Potable water should meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water

Regulations (Title 40, Code of Federal Regulations, Part 141). Potable water in facilities outside the United States should meet comparable standards of the European Union, Japan, the World Health Organization, or other authorities. Drains should be of adequate size and provided with an air break or suitable mechanical device to prevent back-siphonage.

Adequate and clean washing and toilet facilities that are easily accessible to working areas should be provided. These should include hot and cold water, soap or detergent, air dryers or single-service towels. Shower facilities should be provided if needed for personnel hygiene and/or reducing the potential of API contamination or cross-contamination.

F. Sewage and Refuse

Sewage, trash, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from the building and immediate premises should be disposed of in a safe, timely, and sanitary manner.

G. Sanitation

Any building used in the manufacture, processing, packing, or holding of APIs and intermediates should be maintained in a clean and sanitary condition.

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. Such written procedures should be followed. Sanitation procedures should apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

Written procedures should also be established for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging materials, labeling materials, intermediates, and APIs. Rodenticides, insecticides, and fungicides should be registered and applied according to the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136), or other locally applicable regulations.

H. Maintenance

Any building used in the manufacture, processing, packing, or holding of APIs and intermediates should be properly maintained and repaired.

IV. PROCESS EQUIPMENT

A. Equipment Design, Size, and Location

Equipment used in the manufacture, processing, packing, or holding of APIs and intermediates should be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

Closed equipment should be used when feasible (i.e., when equipment is located outdoors or in uncontrolled manufacturing environments) to provide adequate protection of APIs and intermediates. When equipment is opened or open equipment is used, appropriate precautions should be taken to prevent contamination or cross-contamination of APIs and intermediates.

B. Equipment Construction and Installation

Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs are not reactive, additive, or absorptive so as to alter the quality and purity of the API and/or intermediate beyond the official or other established specifications. Any substances required for operation, such as lubricants, heating fluids, or coolants, should not contact raw materials, packaging materials, intermediates, or APIs so as to alter the quality and purity of APIs and intermediates beyond the official or other established specifications.

Where feasible, equipment should be designed, constructed, and installed to allow for ease of cleaning, and, as applicable, sanitization. Qualification of equipment should ensure that:

- It is installed according to approved design specifications, regulatory codes, and the equipment manufacturers' recommendations; and

- The equipment operates within limits and tolerances established for the process.

C. Equipment Cleaning and Maintenance Procedures

Written procedures should be established and followed for cleaning and maintaining equipment, including utensils and storage vessels, used in the manufacture, processing, packing, or holding of APIs and intermediates. Procedures should, at a minimum, include:

- Assigning responsibility for cleaning and maintaining equipment;

- Establishing maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

- Developing a complete description of the methods and materials used to clean and maintain equipment and, when necessary, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning and maintenance;

- Removing or obliterating previous batch identification;

- Protecting clean equipment from contamination prior to use;

- Inspecting equipment for cleanliness immediately before use, if practical; and

- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning.

D. Equipment Cleaning Methods

Equipment and utensils should be cleaned, held and, where necessary, sanitized at appropriate intervals to prevent contamination or cross-contamination that would alter the quality or purity of the API or intermediate beyond the official or other established specifications.

Dedicated equipment should be cleaned at appropriate intervals to prevent the build-up of objectionable material or microbial growth. As processing approaches the purified API, it is important to ensure that incidental carryover of contaminants or degradants between batches does not adversely impact the established impurity profile. However, this does not generally apply to biologic APIs, where many of the processing steps are accomplished aseptically and where it is often necessary to clean and sterilize equipment between batches.

Nondedicated equipment should be thoroughly cleaned between different products and, if necessary, after each use to prevent contamination and cross-contamination. If cleaning a specific type of equipment is difficult, the equipment may need to be dedicated to a particular API or intermediate.

The choice of cleaning methods, cleaning agents, and levels of cleaning should be established and justified. When selecting cleaning agents (e.g., solvents) the following should be considered:

- The cleaning agent's ability to remove residues of raw materials, precursors, by-products, intermediates, or APIs;

- Whether the cleaning agent leaves a residue itself; and

- Compatibility with equipment construction materials.

E. Validation of Equipment Cleaning Methods

Equipment cleaning methods should be validated, where appropriate. In general, cleaning validation efforts should be directed to situations or process steps where contamination or incidental carryover of degradants pose the greatest risk to API quality and safety. In early synthesis steps, it may be unnecessary to validate cleaning methods where residues are removed by subsequent purification steps.

Validation of cleaning methods should reflect actual equipment use patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a worst-case API or intermediate can be selected for purposes of cleaning validation. The worst-case selection should be based on a combination of potency, toxicity, solubility, stability, and difficulty of cleaning.

The cleaning validation protocol should describe the equipment to be cleaned, methods, materials, and extent of cleaning, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples (rinse, swabs) to be obtained, and how they are collected, labeled, and transported to the analyzing laboratory.

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).

Validated analytical methods sensitive enough to detect residuals or contaminants should be in place. 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 may be established based on the minimum known pharmacological or physiological activity of the API or its most deleterious component.

Equipment cleaning and sanitization studies should address microbiological and endotoxin contamination for those processes intended or purported to reduce bioburden or endotoxins in the API, or other processes where such contamination may be of concern (e.g., nonsterile APIs used to manufacture parenteral products).

Cleaning procedures should be checked by appropriate methods after validation to ensure these procedures remain effective when used during routine production. Where feasible, equipment should be examined visually for cleanliness. This may allow detection of gross contamination concentrated in small areas that could go undetected by analytical verification methods.

F. Clean in Place Methods

Where feasible, clean in place (CIP) methods should be used to clean process equipment and storage vessels. CIP methods might include fill and soak/agitate systems, solvent refluxing, high-impact spray cleaning, spray cleaning by sheeting action, or turbulent flow systems.

CIP systems should be subjected to cleaning validation studies to ensure that they provide consistent and reproducible results. When practical, equipment in CIP systems should be disassembled during cleaning validation to facilitate inspection and sampling of inner product surfaces for residues or contamination, even though the equipment is not normally disassembled during routine use.

Once CIP systems are validated, appropriate documentation should be maintained to show that critical parameters (e.g., time, temperature, turbulence, cleaning agent concentration, rinse cycles) are achieved with each cleaning cycle.

G. Automatic, Mechanical, Electronic, and Computer Equipment

Automatic, mechanical, or electronic processing equipment, or other types of equipment, including computers, used in the manufacture of APIs and intermediates should be routinely calibrated, inspected, and checked to ensure proper performance. Written records of those calibration checks and inspections should be maintained.

Written procedures should be established for:

- System operations;
- System qualification and validation;
- Corrective actions to be taken in cases of malfunctions;
- Detecting and recording errors and implementing corrections;
- Restarting the system and recovering data;
- Authorizing, implementing, and recording changes; and

- Use of electronic signatures.

Systems should be appropriately qualified and validated to demonstrate the suitability of the hardware and software to perform assigned tasks in a consistent and reproducible manner. The depth and scope of validation should depend on the diversity, complexity, and criticality of the system.

All changes to a system should be approved by the quality control unit in advance and performed by authorized and competent personnel. Records should be kept of all changes including modifications and enhancements to the hardware, software, and any other critical components of the system to demonstrate that the modified system is maintained in a validated state.

Procedures should be established to prevent unauthorized entries or changes to existing data. Systems should identify and document the persons entering or verifying critical data. Input to and output from the computer or related system should be checked for accuracy at appropriate intervals. Where critical data are entered manually, there should be an additional check on the accuracy of the entry. This may be performed by a second operator or by the system itself. Appropriate controls should be exercised over computers and related systems to ensure that changes in master production and control records or other records are made only by authorized personnel.

A back-up system should be available to respond to system breakdowns or failures that result in permanent loss of critical records. Back-ups may consist of hard copies or other forms (e.g., tapes or microfilm) that ensure back-up data are exact, complete, and secure from alteration, inadvertent erasure, or loss.

V. CONTROL OF RAW MATERIALS

A. General Controls

Written procedures should be established describing the purchase, receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of raw materials. Such procedures should be followed.

Raw materials should be handled and stored in a manner to prevent contamination and cross-contamination. Bagged and boxed raw materials should be stored off the floor and suitably spaced to permit cleaning and inspection. Raw materials that are stored outdoors should be in suitable containers. Identifying labels should remain legible and containers should be appropriately cleaned before opening to prevent contamination.

For solvents or reagents delivered in bulk vessels (e.g., tanker trucks), a procedural or physical system, such as valve locking or unique couplings, should be used to prevent accidental discharge of the solvent into the wrong storage tank.

Each container or grouping of containers of raw materials should be assigned and identified with a distinctive code, lot, or receipt number. This code should be used in recording the disposition of each lot. A system should be in place to identify each lot's status. Large containers (e.g., tanks, silos) that are used for storing raw materials, including their attendant manifolds, filling and discharge lines, should be appropriately identified.

B. Receipt, Sampling, Testing, and Approval of Raw Materials

Upon receipt and before acceptance, each container or grouping of containers of raw materials should be examined visually for appropriate labeling, container damage, seal integrity (where appropriate), and contamination. Raw materials should be held under quarantine until they have been sampled, tested or examined, as appropriate, and released for use.

Representative samples of each shipment of each lot should be collected for testing or examination in accordance with an established procedure. The number of containers to sample and the sample size should be based upon appropriate criteria (e.g., raw material variability, confidence levels, degree of precision desired, past quality history of the supplier, and the quantity needed for analysis). Raw material containers selected for sampling should be opened, sampled, and resealed in a manner that prevents contamination of their contents and of other raw materials. Sample containers should be properly identified.

At least one test should be conducted to verify the identity of each raw material. A supplier's certificate of analysis might be used in lieu of performing other testing provided that the manufacturer has a system in place to evaluate vendors and establishes the reliability of the supplier's test results at appropriate intervals. For hazardous or highly toxic raw materials, where on-site testing may be impractical, suppliers' certificates of analysis should be obtained showing that the raw materials conform to specifications. In addition, the identity of these raw materials should be confirmed by examination of containers and labels. The lack of on-site testing for hazardous raw materials should be documented.

C. Use and Reevaluation of Approved Raw Materials

Approved raw materials should be stored under suitable conditions, and where appropriate, rotated so that the oldest stock is used first. Raw materials should be reevaluated, as necessary, to determine their suitability for use (e.g., after prolonged storage or after exposure to heat or high humidity).

D. Rejected Raw Materials

Rejected raw materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

E. Control of Recovered Solvents, Mother Liquors, and Second Crops

Written procedures should be established for the recovery of solvents, mother liquors, second crops or other materials. These should include adequate tests and controls to ensure that recovered materials are suitable for use in manufacturing processes and do not adversely affect the quality of APIs and intermediates.

Solvents may be recovered and reused in the same process or in different processes, provided that the recovery procedures are validated to ensure that recovered solvents meet appropriate standards before reuse or commingling with other approved materials. The quality of solvent mixtures should be monitored at suitable intervals.

Mother liquors may be reused provided that the quality of the API or intermediate is not adversely affected by their reuse. Procedures for secondary recovery of reactants, intermediates, or the API should ensure that these recovered materials meet specifications suitable for their intended use.

The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented in batch production records.

F. Process Water Quality

Water used in the production of APIs should be routinely tested and, at a minimum, meet the standards for potable water, as stated in the United States Environmental Protection Agency's (EPA) National Primary Drinking Water Regulations (NPRDWR) or comparable standards of other authorities such as the European Union, Japan, or the World Health Organization. The potable water supply, regardless of source, should be assessed for chemicals that may affect the API process. Information should be periodically sought from local authorities concerning potential contamination by pesticides or other hazardous chemicals.

Water of suitable quality, with tighter chemical and microbiological quality specifications, should be used during certain process steps (e.g., cell cultures, final crystallization and isolation) and during early process steps if impurities that affect API quality are present in the water and cannot be removed in later steps. For example, if water is used for a final wash of a filter cake, or if the API is crystallized from an aqueous system, the water should be suitably treated (e.g., deionization, ultrafiltration, reverse osmosis, or distillation) and routinely tested to ensure compliance with appropriate chemical and microbiological specifications. If used for final rinses

during equipment cleaning, the water should be of the same quality as that used in the manufacturing process.

Water used in the final isolation and purification steps of nonsterile APIs intended for use in the preparation of parenteral products should be tested and controlled for bioburden and endotoxins.

Where water is treated to achieve an established quality, the treatment process and associated distribution systems should be qualified, validated, maintained, and tested following established procedures to ensure water of the desired quality.

VI. PRODUCTION AND PROCESS CONTROLS

A. Written Procedures and Deviations

Written production and process control procedures should be established and followed to ensure that APIs and intermediates have the quality and purity they purport or are represented to possess. These procedures, including any changes, should be drafted, reviewed, and approved by the responsible organizational units and reviewed and approved by the quality control unit. The written procedures should be reviewed at defined intervals and updated whenever necessary. Outdated procedures should be withdrawn from circulation and archived.
Production and process control procedures should be followed in the execution of the various production and process control functions and should be documented promptly. Deviations from written procedures should be documented and explained.

B. Raw Material Weighing and Measuring

Raw materials used for manufacturing APIs and intermediates should be weighed or measured as appropriate to maintain their identity, quality, and purity. Suitable equipment and procedures should be used during these activities to prevent raw material contamination or cross-contamination. Weighing and measuring devices should be of suitable accuracy for the intended use. Where necessary, they should be calibrated to ensure accurate results within appropriate ranges.

Raw materials subdivided for later use in manufacturing operations should be transferred into suitable containers and appropriately labeled with the following information:

- Material name and item code;
- Receiving or control number; and
- Weight or quantity of raw material in the new container.

Weighing, measuring, or subdividing operations for raw materials should be adequately supervised. Raw materials should be verified prior to use to ensure that they are those specified in the batch record for the intended API or intermediate.

C. Calculation of Yield

Actual yields and percentages of expected yields should be determined at the conclusion of each appropriate phase of manufacturing or processing of an API or intermediate. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data.

Deviations from expected yields should be investigated and documented. Investigations should include:

- Determining the disposition of affected lots; and
- Taking corrective action, where needed, to minimize the likelihood of problem recurrence.

D. Equipment Identification

Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an API or intermediate should be identified appropriately. This can be accomplished by identifying individual vessels, documentation, computer control systems, or alternative means.

Batch production records should identify the major equipment used in the manufacture of each batch of an API and intermediate.

E. In-Process Controls, Sampling/Testing of APIs and Intermediates

Written procedures should be established and followed that describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on valid data and scientifically sound sampling practices. Sampling should be conducted in an area and using procedures designed to prevent contamination of the sampled material and other APIs or intermediates. Procedures should be established to ensure the integrity of samples after collection. Each sample should be labeled to establish its identity.

Written procedures should be established to monitor the progress and control the performance of those manufacturing processes that may cause variability in the quality characteristics of APIs and

intermediates. In-process controls and specifications should be derived from laboratory-, or pilot-scale batches and may be adjusted later based on data obtained from full-scale production batches.

The type and extent of in-process controls should depend on several considerations, including:

- The nature of the API or intermediate being manufactured
- The reaction or process step being conducted; and
- The degree to which the step introduces variability in the process.

Less stringent in-process controls may be appropriate in early processing steps whereas tighter controls should be applied to later synthesis, isolation, and purification steps.

In-process tests may be performed by qualified production department personnel and the process adjusted without prior quality control approval, provided adjustments are made within preestablished limits approved by the quality control unit. All in-process tests and results should be documented in the batch record.

APIs and intermediates failing to meet established specifications should be rejected and held under quarantine until an investigation determines the appropriate disposition of the materials. Materials to be reprocessed or reworked should be appropriately identified.

F. Time Limits on Production of APIs and Intermediates

When appropriate, time limits for the completion of manufacturing steps should be established to ensure the quality of APIs and intermediates. Deviations from established time limits should not compromise the quality or purity of the API or intermediate. Such deviations should be documented and explained.

Written procedures should be established for intermediates that are stored before further processing. Where necessary, these procedures should specify appropriate storage conditions, packaging materials, temperature, time, and protection from humidity and light when these are critical for maintaining the quality of the intermediate.

G. Control of API Contamination

Appropriate measures should be taken during final filtration and isolation steps to avoid contamination or cross-contamination of APIs. Such measures should include:

- Use of equipment designed to minimize contamination;

- Use of adequately cleaned and maintained equipment, and where necessary, dedicated equipment;

- Location of equipment in a controlled environment;

- Use of suitably filtered liquid and gaseous materials (e.g., gases that are used to vent or blanket dryers); and

- Use of adequately purified solvents and other purified raw materials.

In addition, special precautions should be taken during drying, milling, micronizing, sieving, blending, and packaging operations due to the contamination risks associated with handling dry powders. Such precautions should include:

- Use of closed systems for isolation and drying, where possible;

- Use of automated powder transfer systems (e.g., vacuum, gravity systems) when charging and discharging vessels; and

- Use of appropriate air handling and dust extraction systems.

When appropriate, written procedures should be established and followed to minimize objectionable microbiological contamination in APIs and intermediates that (1) are of biologic origin; (2) are sensitive to microbiological deterioration; or (3) have established microbiological specifications.

Written procedures should be established and measures taken to control bioburden and endotoxin contamination of nonsterile APIs intended for use in the preparation of parenteral drug products.

H. Blending of APIs and Intermediates

In-process blending (e.g., collecting several centrifuge loads in a single dryer or blender, blending of several intermediate batches for use in subsequent process steps, blending of tailings) should be adequately controlled and documented. Appropriate specifications should be established for in-process materials to be blended to ensure the quality of the blend.

Blending of batches or lots that individually do not conform to purity specifications with other lots that do conform for the purpose of salvaging materials or disguising defects should be avoided

When blending several API batches to increase batch size,

- Each batch incorporated into the blend should meet established purity specifications;
- Each batch incorporated into the blend should have been produced by the same process;
- The lot or control number assigned to each blend should allow traceability back to the individual batches that make up the blend; and
- The expiration or retest date assigned to the blended API batch should be based on the manufacturing date of the oldest batch in the blend.

For dry blended APIs, the maximum lot size for final API blends should be limited to the maximum working capacity of the largest blender used.

Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the blended batch. Validation should include testing for critical attributes (e.g., particle size distribution, bulk, and tap density) that may be affected by the blending process.

VII. PACKAGING AND LABELING CONTROLS

A. Materials Examination and Usage Criteria

There should be written procedures describing the receipt, preparation, identification, storage, handling, sampling, examination, and/or testing of API labeling and packaging materials. Such written procedures should be followed and documented. Labeling and packaging materials should be representatively sampled and examined or tested, as appropriate, before use.

All labeling and packaging 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. Records should be maintained for each shipment of labeling and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

Labeling for each different API form or grade should be stored separately with suitable identification. Such storage should provide adequate security to avoid mix-ups. If gang printed labels are used for different APIs, these should be adequately differentiated by size, shape or color. If cut labels are used, appropriate measures should be taken to prevent label mix-ups.

Obsolete and outdated labeling should be destroyed. Other obsolete packaging materials should be destroyed or otherwise disposed of in a way that precludes mixups with currently acceptable materials.

Printing devices used to print labels during packaging operations should be monitored to ensure that all imprinting conforms to the print specified in the batch production record.

B. API Label Issuance

Strict controls should be exercised over labels issued for use in labeling operations. Labels issued for a batch should be carefully examined for proper identity and conformity to the specifications in the master or batch production records. The results of this examination should be documented.

Quantities of labels issued, used, and returned should be reconciled. Discrepancies should be investigated and documented.

C. Packaging and Labeling Operations

Written procedures should be established to ensure that correct labels, labeling, and packaging materials are used for APIs. Such procedures should be followed and documented.

Physical or spatial separation from other API operations should be provided to prevent mixups and contamination. Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not required for the next packaging run have been removed. This inspection should be documented.

Each API should be identified with a lot or control number that permits determination of the history of its manufacture and control. Packaged and labeled APIs should be examined to ensure that containers and packages in the lot bear the correct label.

API containers that are shipped outside of the manufacturer's control should be sealed in a manner that alerts the recipient of possible tampering if the seal is breached or missing.

D. API Packaging Materials

API packaging materials should not be reactive, additive, or absorptive so as to alter the quality or purity of the API beyond the official or established requirements. Packaging materials should provide adequate protection against deterioration or contamination that may occur during transportation and recommended storage of the API.

API packaging materials should be cleaned, as appropriate, and where indicated by the nature of the API, sanitized, to ensure that they are suitable for their intended use. Standards or

specifications, methods of testing, and, where indicated, methods of cleaning, sanitizing, and processing API packaging materials should be written and followed.

E. Expiration or Retest Dating

Antibiotic APIs and all biologic APIs should be labeled with an expiration date. For other APIs, the container label or certificate of analysis (COA) should specify an appropriate expiration date or retest date to ensure the quality of the API at the time of use. Expiration or retest dates should relate to any storage conditions stated on the label and should be supported by appropriate stability studies, as stipulated in Section IX.C.

Storage conditions should be specified on the label of API containers when it is critical to maintain such conditions to ensure the quality of the API. Where applicable, labeled storage conditions should comply with standard definitions for "Freezer," "Cold," or "Controlled Room Temperature," as defined in the United States Pharmacopeia (USP) or guidelines of the International Conference on Harmonisation (ICH). Statements of specific storage conditions should be used instead of more general terms such as “room temperature” when it is critical for maintaining the quality of APIs.

For most biotechnological and biologic APIs, precisely defined storage temperatures should be established and stated on the label. The label on each container should also bear any warnings to protect the contents from excessive heat, freezing, light or moisture.

VIII. HOLDING AND DISTRIBUTION OF APIs AND INTERMEDIATES

A. Warehousing Procedures

Written procedures describing the warehousing of APIs and intermediates should be established and followed. They should include:

- Storage under a quarantine system before release by the quality control unit; and

- When appropriate, storage under specified conditions of temperature, humidity, and light so that the quality and purity of APIs and intermediates are not adversely affected.

B. Distribution Procedures

Written procedures should be established and followed describing the distribution of APIs and, where applicable, intermediates. They should include:

- Distribution of the oldest approved stock of an API or intermediate before distribution of newer stock with deviations recorded and explained;

- A system by which the distribution of each lot of API or intermediate can be readily determined to facilitate its recall if necessary; and

- Transportation of APIs and intermediates in a manner that does not adversely affect their purity or quality.

IX. LABORATORY CONTROLS

A. General Controls

Specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, including changes in same, should be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. Laboratory controls should be followed and documented at the time of performance. Deviations from written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms should be documented and justified.

Laboratory controls should include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures to ensure that raw materials, intermediates, APIs, and containers conform to established standards of quality and purity.

Procedures should be established to determine conformance to appropriate written specifications for the acceptance of each lot of raw materials, containers, intermediates, and APIs. Such procedures should also cover appropriate sampling and retesting of any materials used in the manufacturing or holding of an intermediate or API that are subject to deterioration or degradation. Laboratory test samples should be representative, properly handled, and adequately identified.

A program should be in place to calibrate or demonstrate suitability of instruments, apparatus, gauges, and recording devices at suitable intervals. The program should contain specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications should not be used.

Secondary laboratory reference standards (e.g., production lots that are further purified and qualified in the laboratory) should be appropriately prepared, identified, stored, and tested, as necessary, to ensure their suitability for use. The suitability of each lot of secondary reference standard should be determined prior to use by comparing against a primary reference standard

obtained from an official source and periodically requalifying each lot in accordance with a written protocol. Primary reference standards need not be tested if stored under conditions consistent with those described in the labeling.

Analytical reagents should be prepared and labeled following established procedures. Retest or expiration dates should be used, as appropriate, for analytical reagents, or standard solutions.

Analytical methods should be validated unless the method employed is set forth in the current revision of the *United States Pharmacopeia/National Formulary, Association of Official Analytical Chemists, Book of Methods*,[2] or other recognized standard references, or detailed in a Drug Master File or approved new drug application and are used unmodified. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

B. Testing and Release for Distribution

Appropriate laboratory tests should be conducted on each lot of API or intermediate to determine satisfactory conformance to established specifications. Intermediates should be tested as appropriate for conformance to specifications.

Microbiological testing should be conducted on each lot of API required to be free of objectionable microorganisms. Appropriate testing should also be conducted on each lot of API required to be pyrogen free or with a specified endotoxin limit (e.g., APIs intended for use in the preparation of parenteral drug products).

Impurity profiles should be established and maintained for each API that identify or quantify each impurity observed (i.e., organic impurities, inorganic impurities, and residual solvents). In general, all impurities at or above 0.1% should be identified.[3] Test procedures for establishing impurity profiles should be written and followed.

Intermediates and APIs failing to meet established standards or specifications should be rejected. Adequate written procedures should be followed for rejected materials that are reprocessed or reworked.

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[2] Copies may be obtained from the Association of Official Analytical Chemists, 2200 Wilson Blvd., Suite 400, Arlington, VA 22201-3301.

[3] See the January 1996 "Guideline for Industry Impurities in New Drug Substances" and the ICH Harmonized Tripartite Guideline "Impurities in New Drug Substances," recommended for adoption at Step 4 of the ICH process on 30 March 1995.

C. Stability Testing

A formal testing program should be established to assess the stability characteristics of APIs. The results of such testing should be used to determine appropriate storage conditions and retest or expiration dates. The testing program should be ongoing and include:

- The number of lots placed on stability per year, sample size, and test intervals;
- Storage conditions for samples retained for testing; and
- Stability indicating test methods.[4]

Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in polyliners within fiber drums, stability samples should be packaged in bags of the same material and in smaller scale drums of similar or identical composition to the market drums.

An adequate number of batches of each API should be tested at suitable intervals to determine an appropriate retest or expiration date. This generally includes samples from the first three commercial size batches, but fewer batches may be appropriate in the initial testing program if data from previous studies or from literature show that the API is stable for at least two years. For those biotechnological/biologic and other APIs having shelf-lives of one-year or less, stability samples should be obtained and tested monthly for the first three months, and at three-month intervals thereafter.

When stability data from pilot-scale batches are used to establish a tentative expiration date:

- The pilot batches should be manufactured by procedures that simulate the final process to be used on a commercial manufacturing scale;
- The quality of the API should represent the material to be made on a commercial scale.

After the initial retest or expiration date has been established, at least one batch of API manufactured during a given year should be added to the stability testing program to detect

[4] This guidance applies to stability testing for active pharmaceutical ingredients. FDA recommends that manufacturers also consult the Agency's February 1987 *Guideline For Submitting Documentation For The Stability Of Human Drugs And Biologics* and the relevant International Conference On Harmonisation (ICH) guidances, including: *Stability Testing of New Drug Substances and Products*, *Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*, and *Light Stability Testing of New Drug Substances And Products*.

changes in the stability profile. Changes in manufacturing site, materials, or manufacturing processes should be evaluated to determine if these changes affect API stability.

D. Reserve Samples

Appropriately identified reserve samples representative of each lot of API should be retained for one year after the expiration date of the lot, or, for APIs having retest dates, three years after the batch is distributed.

Reserve samples should consist of at least twice the quantity necessary for all tests required to determine whether the API meets its established specifications. The samples should be stored in containers that would be equivalent or more protective than the marketed packaging system. Representative reserve samples should be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve samples. Any evidence of deterioration should be investigated. The results of the examination should be documented and maintained.

E. Laboratory Animals

Animals used in testing raw materials, in-process materials, intermediates, or APIs for compliance with established specifications should be maintained and controlled to ensure their suitability for their intended use. Animals should be identified and adequate records maintained showing the history of their use.

X. RECORDS AND REPORTS

A. General Controls

Any production, control, or distribution record specifically associated with a batch of API should be retained for at least one year after the expiration date of the batch. For APIs with retest dates, records should be retained for at least three years after the batch is completely distributed to either internal or external recipients.

Records should be maintained for all raw materials and API containers for at least one year after the expiration date of the batch. For APIs with retest dates, these records should be retained for at least three years after the API batch is completely distributed to either internal or external recipients.

All records or copies of such records should be readily available for authorized inspection and copying by FDA during the retention period at the establishment where the activities described in

such records occurred. Records kept off site should be promptly retrievable by electronic or other means.

Records may be retained either as originals, electronic records, or as true copies, such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and copying equipment should be readily available.

Written records should be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each API to detect the need for changes in specifications or manufacturing or control procedures. Written procedures should be established and followed for such evaluations and should include provisions for:

- A review of a representative number of batches, whether approved or rejected, and their associated records; and

- A review of process changes, stability data/protocols, complaints, recalls, returned or salvaged APIs, and deviation investigations conducted for the API being evaluated.

Procedures should be established to ensure that designated officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted, any recalls, reports of inspectional observations issued by the FDA, or regulatory actions relating to CGMPs brought by the Agency.

Electronic records and electronic signatures used under this section should comply with Part 11 of Title 21 of the Code of Federal Regulations.

B. Equipment Cleaning and Use Record

A written record should be maintained of major equipment cleaning and maintenance (except routine maintenance such as lubrication and adjustments), that shows the date, time, API or intermediate, the lot number of each batch processed, and the person who performed the cleaning.

Where equipment is dedicated to manufacturing one API or intermediate and lots or batches are manufactured in numerical sequence, the records of cleaning, maintenance, and use should be part of the batch record or maintained separately (e.g., equipment log books). The persons performing and checking the cleaning and maintenance should date and sign or initial the record showing that the work was done. Entries in the record should be in chronological order.

C. Raw Material, API Packaging Materials, and Labeling Records

These records should include the following:

- The identity and quantity of each shipment of each lot of raw materials, intermediates, API packaging materials, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code; and the date of receipt;

- The name and location of the manufacturer, if different from the supplier;

- The results of any test or examination performed and the derived conclusions;

- Documentation of the examination and review of labeling and API packaging materials for conformity with established specifications; and

- The disposition of rejected raw materials, API packaging materials, and labeling.

D. Master Production and Control Records

Master production and control records for each API and intermediate, including each batch size thereof, should be prepared, dated, and signed by one person and independently checked, dated, and signed by at least one other person. The quality control unit should review and approve master production and control records. The preparation of master production and control records should be described in a written procedure and followed.

Master production and control records should include:

- The name of the API or intermediate and an identifying reference code, if applicable;

- A complete list of raw materials or intermediates designated by names or codes sufficiently specific to indicate any special quality characteristics;

- An accurate statement of the quantity and unit of measure of each raw material or intermediate (variations in the amounts of raw materials or intermediates should be reasonable and justified);

- A statement of expected weights or measures at appropriate phases of processing;

- A statement of expected yields, including the maximum and minimum weights or measures, or the percentages of expected yield beyond which investigation is initiated;

- The manufacturing location and the major equipment to be used;

- Complete manufacturing instructions and, where appropriate, special notations and precautions to be followed, or cross references to same;

- Any sampling instructions and in-process controls with their limits, where appropriate; and

- Requirements for storage of APIs or intermediates, including the packaging materials, labeling, and special storage conditions, where applicable.

E. Batch Production and Control Records

Batch production and control records should be prepared for each batch of API or intermediate produced and should include complete information relating to the production and control of each batch. These records should include an accurate reproduction or reference to the appropriate master production and control record, checked for accuracy, dated, and signed.

Batch records should include documentation that each significant step in the production of the batch was accomplished including:

- Dates, and where appropriate, times;

- Identity of individual major equipment used;

- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed/reworked materials used during manufacturing;

- In-process and laboratory control results;

- A statement of the actual yield compared against an expected yield at appropriate phases of manufacture;

- Description of API and intermediate packaging and labeling;

- Any sampling performed;

- Signatures of the persons performing and directly supervising or checking each significant step in the operation;

- Any deviation investigations conducted or reference to that investigation if stored separately; and

- Results of release testing.

F. Production Record Review

Written procedures should be established and followed for the review and approval of batch production, control, and laboratory records, including packaging and labeling, to determine compliance of the API or intermediate with established specifications before a batch is released or distributed.

Batch production and control records for critical process steps should be reviewed and approved by the quality control unit before a batch is released or distributed. Where the quality control unit does not review noncritical process steps, the review should be performed by qualified production personnel or other units following procedures approved by the quality control unit.

Written procedures should be established and followed for investigating unexplained discrepancies, including:

- Results out of the expected yield range established in master production and control records;

- Failure of a batch to meet specifications; and

- Any out-of-specification (OOS) test results.

The investigation should extend to other batches of the API or other batches that may have been associated with the specific failure or discrepancy, regardless of whether the batch has already been distributed.

A written record of the investigation should be prepared and should include:

- The reason for the investigation;

- A summary of the investigation conducted, including all laboratory tests and results;

- Scientifically sound and appropriate justification for excluding any OOS

laboratory result;

- For laboratory results found invalid, the subsequent laboratory results supporting the final determination of conformity to all appropriate specifications for acceptance;

- The conclusions and corrective actions taken regarding batches associated with the failure or discrepancy; and

- The signature(s) and date(s) of the person(s) responsible for approving the record of investigation.

G. Laboratory Records

Laboratory records should include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing including the source, quantity, lot number or other distinctive code, date sample was taken, and date the sample was received for testing;

- A statement of or reference to each method used in testing the sample;

- A statement of the weight or measure of sample used for each test;

- A complete record of all raw data secured during each test, including graphs, charts, and spectra from laboratory instrumentation, properly

- identified to show the specific raw material, intermediate, or API, and lot tested;

- A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors;

- A statement of the test results and how they compare with established standards of quality and purity for the raw material, intermediate, or API tested;

- The initials or signature of the person who performs each test and the date(s) the tests were performed; and

- The initials or signature of a second person showing that the original records

have been reviewed for accuracy, completeness, and compliance with established standards.

Complete records should be maintained for:

- Any modifications to an established analytical method, to include the reason for the modification and data to verify that the modification produces results that are at least as accurate and reliable as the established method;
- Preparation and testing of laboratory reference standards, reagents, and standard solutions;
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;
- All stability testing performed on APIs; and
- OOS investigations.

H. Distribution Records

Distribution records should contain the name of the API or intermediate, the name and address of the consignee, date, quantity shipped, and lot or control number.

I. Complaint Files

Written procedures describing the handling of all written and oral complaints regarding an API should be established and followed. Similar procedures should be established for complaints involving marketed intermediates. These procedures should provide for the quality control unit to review of all complaints involving the possible failure of an API to meet any of its specifications, determine the need for an investigation, and ascertain whether the complaint represents a serious and unexpected event that would require notification to users of the API.

A written record of each complaint should be maintained in a file designated for APIs. The file should be kept at the establishment where the API was manufactured, processed, or packed or at another facility if the written records in such files are readily available for inspection at that other facility. Complaint records should be maintained for at least one year after the expiration date of the API, or one year after the date the complaint was received, whichever is longer. For APIs with retest dates, such written records should be maintained for at least three years after the batch is distributed. The written record should include the name of the API, batch or lot number, name and address of the complainant, nature of complaint, and reply to the complainant.

If an investigation is conducted in response to a complaint, the record should include the findings of the investigation and any conclusions or corrective actions taken. The record (or copy) of the investigation should be kept at the establishment where the investigation occurred. If an investigation is not conducted, the written record should include the reason that an investigation was found to be unnecessary, and the name of the responsible person making such a determination.

J. Returned APIs and Intermediates

Written procedures for the receipt, holding, testing, and disposition of returned APIs and intermediates should be established and followed. These procedures should provide for the identification and holding of returned APIs and intermediates. Where an API or intermediate is placed back into inventory, the reason for its return should not have been due to quality issues, and the integrity of the returned material should have been verified. If the quality or purity of the API or intermediate cannot be ensured, the returned material should be destroyed, reprocessed, or reworked as appropriate. If the reason for the return implicates associated batches, an appropriate investigation should be conducted as described in Section XII.F.4.

Records of returned APIs and intermediates should be maintained and should include the name, batch or lot number, reason for the return, quantity returned, date of disposition, and ultimate disposition.

K. API and Intermediate Salvaging

APIs and intermediates that have been subjected to improper storage conditions, including extremes in temperature and humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures should not be salvaged.

Whenever there are doubts that APIs and intermediates have been subjected to adverse conditions described above, salvaging operations should only be conducted if there is both (1) evidence from inspection of the premises that the APIs and intermediates and their associated packaging were not subjected to improper storage condition and (2) evidence from laboratory tests and assays that the APIs and intermediates meet all applicable standards of quality and purity.

XI. VALIDATION

A. Process Validation Strategy

A written program should be established and followed for validating the manufacturing processes for all APIs. Validation studies should ensure that a specific manufacturing process is capable of

performing in a reliable and consistent manner and results in a homogeneous API that consistently meets predetermined specifications.

Validation should embrace steps in the processing of APIs that are critical to the quality and purity of the final API, and should include:

- Definition of the API in terms of its critical quality attributes. Among the attributes that should be considered are chemical purity; qualitative and quantitative impurity profiles; physical characteristics such as particle size, bulk and tap density; polymorphic forms; moisture and solvent content; homogeneity; and microbial quality (if the product is susceptible to microbial contamination).

- Identification of process parameters that could affect the critical quality attributes of the API. Critical parameters should be determined by scientific judgement and typically should be based on knowledge derived from research, scale-up batches, or manufacturing experiences.

- Determination of the range for each critical process parameter expected to be used during routine manufacturing and process control. Data to substantiate the ranges for critical process parameters generally should be obtained from laboratory- or pilot-scale batches, unless a specific parameter can only be determined from a production-scale batch.

Examples of processing steps that could be defined by the API manufacturer as critical include:

- Phase changes, such as dissolution or crystallization;

- Phase separation, such as filtration or centrifugation;

- Steps that cause chemical changes;

- Steps that alter temperature or pH;

- Mixing of multiple raw materials; and

- Steps that cause changes in surface area, particle size, bulk and tap density or homogeneity.

Critical process parameters (e.g., reaction times, reaction temperatures, reactant ratios, concentrations, pressures, pH, and impurity levels) 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.

Process validation should confirm that the impurity profile for each API is within the limits specified and is comparable to the profile determined during process development or for batches used for pivotal/toxicological studies.

B. The Validation Protocol

A written validation protocol should be established that specifies how process validation will be conducted. The protocol should be reviewed and approved by the quality control unit and other designated organizational units.

The validation protocol should include the following:

- Purpose and scope of the validation;
- Functions and responsibilities of all organizational units involved in the validation;
- Type of validation to be conducted with appropriate justification for type chosen;
- Number of process validation runs;
- Quality of materials used in the process (e.g., recovered vs. fresh solvents);
- Description of the process (e.g., discussion of the chemistry, unit operations, process flow diagram);
- All major process equipment used, its type/design, and its installation and operational qualification (IQ/OQ);
- The critical quality attributes of the API;
- The critical process parameters and operating ranges;
- Sampling plans (i.e., sampling points, frequency, quantities, and procedures for collecting samples);
- Specifications and test data to be collected;
- Acceptance criteria needed to conclude that the validation has been successful; and

- Steps to follow in the event of a process validation failure.

The above information need not be incorporated in the validation protocol if the protocol makes specific reference to other documents that contain the information (e.g., COA's, development reports, and IQ/OQ reports). Any changes to the validation plan should be documented with appropriate justification.

C. Prospective Validation

Prospective validation should be conducted prior to the commercial distribution of an API produced by a new or substantially modified process. This validation approach should involve obtaining and evaluating documented processing and analytical control information for multiple batches manufactured, sampled, and tested according to a preestablished validation plan.

When prospectively validating a process, data from laboratory- and/or pilot-scale batches should identify critical quality attributes and specifications, critical steps, control ranges, and in-process tests. Scale-up batches could be used to generate data to confirm or refine earlier work, and production-scale batches should provide data showing consistency of the process.

The number of process runs should depend on the complexity of the process or the magnitude of the process change being considered. Although three consecutive, successful production lots should be used as a guide, there could be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). If a validation lot fails for reasons unrelated to process performance (e.g., power failure or equipment breakdown), that lot should be removed from the validation study and an additional validation run conducted.

Validated analytical methods capable of quantifying API quality attributes should be used during process validation. Resulting data should be evaluated and included in a validation report approved by the same organizational units that approved the protocol.

D. Concurrent Validation

FDA considers concurrent validation to be a subset of prospective validation. The Agency recognizes that in a limited number of cases it may be impossible to complete validation of an API process in a timely manner when data from replicate production runs are unavailable because:

- Only a limited number of API batches intended for clinical or orphan drug products have been produced;

- API batches are produced infrequently (e.g., limited market demand, complex multi-step API processes with long completion times); or

- APIs batches are produced by a modified process (e.g., a validated process goes outside the proven acceptable range of a critical operating parameter and the batch is subjected to intensive analytical tests).

In such cases, firms should do all of the following:

- Document the reasons for not completing process validation before shipment of the API;

- Perform all of the elements of prospective validation, as discussed in Section XIII.C., exclusive of replicate production run testing, before releasing any batch for distribution;

- Conduct intensive in-process monitoring and testing, along with intensive testing of each API batch, to show that each production run resulted in an API meeting its predetermined quality characteristics and specifications (such data should also be assessed under the validation protocol to determine consistency of the process);.

- Provide for the Quality Control unit to evaluate batch production records, in-process controls, and analytical data from each process run to determine whether each batch should be released.

The level of intensive in-process and final API testing should be greater than levels for validated routine production runs, and should only be reduced to routine levels after the process has been determined to be validated. In addition, data from production runs that are evaluated as part of the validation studies should encompass the operating ranges that are approved for use during routine process control.

The Agency cautions that this validation approach should be applied with discretion so as not to:

- Unduly delay completion of, or avoid performing, meaningful validation; or

- Distribute API batches manufactured before completion of validation for a prolonged period of time.

This approach should not be viewed as a viable alternative where the number and frequency of API production runs permit timely completion of validation prior to API distribution. If analysis of data shows that the process used to manufacture the distributed batches was not, in fact, validated, no additional batches should be distributed until corrections have been implemented and the process has been determined to be validated.

E. Retrospective Validation

Retrospective validation could be conducted for a well-established process that has been used without significant changes (e.g., changes in raw materials, equipment, systems, facilities, or in the production process) that affect the critical quality attributes of the API. This validation approach should be used only when there is sufficient history on past API batches to demonstrate the process consistently produces acceptable products, and where:

- Critical quality attributes and critical process parameters have been identified and documented;
- Appropriate in-process specifications and controls have been established and documented;
- There have not been excessive process/product failures attributable to causes other than operator error or equipment failure unrelated to equipment suitability; and
- Impurity profiles have been established for the existing API.

In addition to the information described in Section XIII.B., the validation protocol should include the batch selection criteria and analytical data that will be evaluated to determine consistency of the process.

The number of batches to review will depend on the process, but, in general, data from 10 to 30 consecutive batches should be examined to assess process consistency. The review should include any batches that failed to meet specifications. All batches within the selected review period should have been manufactured by the same process and have the same documented history of controls and tests as current APIs. Additional testing of retained samples may be warranted to obtain the necessary data to retrospectively validate the process.

Data obtained should be evaluated by appropriate personnel, and a final validation report summarizing the results and appropriate conclusion should be prepared. This report should be reviewed and approved by the organizational units that approved the original protocol.

Retrospective validation could also be employed to provide additional data to supplement prospective validation and either build confidence in a particular manufacturing process or impugn it as test results are received.

XII. CHANGE CONTROL/REVALIDATION

A. Change-Control System

To provide mechanisms for ongoing process optimization and ensure a continuing state of process control, a formal change control system should be established to evaluate and approve proposed changes to specifications, test procedures, raw materials, facilities, support systems, equipment (including computer hardware), processing steps, packaging materials, and computer software.

The change-control program should include procedures to:

- Prevent unauthorized modifications to a validated system;
- Evaluate proposed changes against development and technology transfer documents;
- Identify and evaluate all proposed changes to assess their potential affects on the API process and determine if, and to what extent, revalidation is needed;
- Ensure that all documents affected by changes are promptly revised; and
- Determine the impact of changes on the critical chemical and physical attributes of the API (e.g., impurity profiles, stability, and particle size).

Any proposals for changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the quality control unit.

Changes implemented to improve process yields should be evaluated carefully to determine if these result in new or higher levels of impurities. The impurity profile of the resulting batches should be comparable to the impurity profile of the API batches used in drug safety and clinical testing. Process changes should also be evaluated to ensure that these do not have an adverse effect on analytical methods due to increased interference caused by new or higher levels of impurities and by-products. Analytical methods should be modified as necessary to ensure they are capable of detecting and quantifying impurities.

Dosage form manufacturers should be notified of changes in the API production process that could affect the critical attributes of the API (e.g., impurity profile, crystal form, particle size, residual solvent content, or stability) and thus have a significant impact upon the dosage forms produced from that API.

B. Change-Control Classification

The change-control program should provide for a classification scheme to evaluate changes in raw materials, manufacturing sites, scale of manufacturing, manufacturing equipment, and production processes. This classification procedure should be used in determining what level of testing, validation, and documentation is needed to justify changes to a validated process.

Changes should be categorized as minor or major depending on the nature and extent of the changes, and the effects these changes could impart on the process. In all cases, scientific judgement should determine what additional testing and validation studies are needed to justify a change in a validated process.

A minor change should be defined as one that is unlikely to have a detectable impact on the critical attributes of the API. Such changes would not shift the process in any discernible manner, and might be implemented with minimal testing and revalidation. For example, "like-for-like" equipment replacements where equipment is repaired to its initial validated state or in which identical or similar equipment is introduced into the process, would unlikely affect the process if adequately installed and qualified.

A major change should be defined as one that would likely significantly affect the critical quality attributes of the API. For example, a change in solvent used for the final crystallization could significantly affect the impurity profile, physical attributes, and other critical quality attributes of the API. Such changes should be justified by additional testing, and if appropriate, revalidation.

XIII. REPROCESSING/REWORKING OF APIs AND INTERMEDIATES

A. Reprocessing by Repeating a Chemical Reaction

Due to the potential for formation of by-products, reprocessing an API or intermediate by repeating a chemical reaction (adding fresh reagents or solvents to unreacted or base material and starting over) should be preceded by a careful evaluation to ensure that the quality of the final API is not adversely impacted.

Where such reprocessing occurs, written process change procedures should be approved by the quality control unit that clearly specify the conditions and limitations of repeating chemical reactions. In addition, the procedures should establish how this type of reprocessing will be evaluated, and what additional tests will be conducted on the reprocessed material to show that the resulting material is of a purity and quality comparable to that normally produced by the process. These tests should include, as appropriate, purity, impurity profiles, stability testing on initial reprocessed lots, and testing for physical attributes.

B. Reprocessing by Physical Manipulations

Intermediates and API batches that occasionally do not conform to specifications for percent transmittance/color, or critical attributes (e.g., purity, impurities, particle size) can be reprocessed by repeating a crystallization step or other physical manipulation steps (e.g., dissolution, filtration, milling, blending) that are part of an established process.

If it becomes necessary to more than occasionally reprocess batches by physical manipulation, a thorough investigation should be conducted and documented to determine the adequacy of the original process. Appropriate actions should be taken to minimize the risk of recurrence. For example, if investigation of the nonconformance and/or review of the process reveals an abnormally high rate of batches that need to be recrystallized, it would be reasonable to incorporate the recrystallization as part of the normal process.

All reprocessing procedures should be reviewed and approved by the quality control unit. These procedures should specify the conditions and limitations for reprocessing by physical manipulations and require an evaluation of each nonconforming batch to determine its suitability for reprocessing. For example, one or more recrystallizations from the final solvent might be justified, but continuous reprocessing of batches until they meet a given quality specification would indicate a problem with the original process. A specific record should be generated to document reprocessing steps and subsequent handling and incorporated into the original batch record.

Appropriate tests should be conducted on reprocessed batches to ensure that reprocessing does not adversely affect the quality or purity of the API or intermediate. These tests should include, as appropriate, purity, physical attributes, and impurity profiles. In all cases, the significance of the nonconformance and its impact on the critical quality attributes of the API or intermediate should determine how much analytical data is sufficient to justify the reprocessing.

Reprocessing operations should be subjected to appropriate evaluation to show that these steps consistently perform the expected functions and result in batches that comply with all established standards, specifications, and characteristics.

C. Reworking of APIs and Intermediates

Reworking batches that do not conform to established standards or specifications by using processing steps that are different from the validated process should involve extensive evaluation and documentation to show that the reworked product is of equivalent quality to that produced by the original process.

Reworking operations should be subjected to appropriate evaluation to show that such reworking does not adversely affect the quality or purity of the API or intermediate. Where routine

analytical methods are inadequate to characterize the reworked batch, alternative methods should be used.

XIV. CONTROL OF CHEMICAL, BIOLOGICAL, AND PHYSICAL CONTAMINANTS

Written procedures should be implemented to prevent objectionable chemical, biological, and physical contamination, including cross-contamination in APIs and intermediates.

Dedicated production, which may include facilities, air handling equipment and/or process equipment, should be employed where both of the following conditions exist:

- Contaminants pose a special danger to human or animal health. In the case of human health, these include, but are not limited to, penicillin, cephalosporins, cytotoxics, toxins, and infectious agents; and

- There are no effective methods for cleaning and removing contaminant residues from buildings, facilities, and equipment to levels below those determined by suitable medical and toxicological assessment to pose no serious health risk to the consumer.

If a reasonable possibility exists that an API or intermediate has been exposed to cross-contamination, the substance should be tested for the presence of the potential contaminant. APIs and intermediates that exceed established limits for such contaminants should not be used in further manufacturing.

XV. APIs FOR CLINICAL TRIALS

A. Quality Assurance Measures

Appropriate quality control measures and CGMP concepts should be applied in the production of APIs for clinical trials with a suitable mechanism for approval of each batch.

The manufacturing practices used in the production of clinical APIs should be consistent with the stage of development of the drug product incorporating the API. Processes and analytical methods should be flexible to provide for changes as knowledge of the API process increases and testing of a drug product progresses from preclinical through clinical stages.

Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials in humans or animals, manufacturers should ensure that the clinical API

is manufactured in qualified facilities using appropriate production and control procedures to ensure the safety, quality, and homogeneity of the API.

B. Quality Control Unit

An independent quality control unit similar to that used in commercial production should be established in clinical production of APIs for the approval or rejection of each batch of API. Some of the testing functions commonly performed by the quality control uit could be performed within other areas.

Quality control measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs. Labeling for APIs intended for clinical trials should be appropriately controlled. Labeling for such APIs should identify the material as intended for investigational use.

C. Equipment and Facilities

During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture clinical API batches, procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use.

Procedures for the use of facilities should ensure that materials are handled in a manner that prevents contamination and cross-contamination.

D. Control of Raw Materials

Raw materials used in early stages of clinical API production should be evaluated by analytical testing, or received with a supplier’s certificate of analysis and subjected to identity testing.

E. Production and Process Controls

Laboratory notebooks or batch records can be used to document the production of clinical APIs. These should include all pertinent production materials, equipment, processing, and scientific observations.

Expected yields might be more variable and less defined than the expected yields used in commercial processes.

F. Process Validation

At early clinical stages, where a single API batch is often produced and where significant processing changes often make batch replication difficult or inexact, only limited process validation is possible.

Concurrent validation might be appropriate in situations where a single or limited number of API batches are produced for clinical trials. This involves obtaining data from extensive in-process and end testing to demonstrate that the instant process run yields an API meeting established specifications and quality characteristics. Process validation should be completed once additional batches are produced under replicated conditions.

Prospective validation should be used when multiple batches are initially produced for clinical trials, even when such batches are produced on a pilot scale or small scale. Once pilot- or small-scale production process are scaled up, the commercial production process should be subjected to full validation studies.

G. Change Documentation

Changes to the process are expected during clinical development as knowledge of the process is gained and the production is scaled up. All process modifications should be adequately documented.

H. Laboratory Controls

All analysis performed to evaluate a batch of API for clinical trials should be scientifically sound.

A system for retaining reserve samples of APIs should be established and followed. This system should ensure that reserve samples are retained for an appropriate lenth of time after approval, termination, or discontinuation of an investigational new drug application (IND), a new drug application (NDA), or biologics license application (BLA). Additional reserve samples should be maintained for API batches used in pivotal toxicological and/or biobatches.

I. Documentation

A system should be in place to ensure that information obtained during the development and production of APIs for clinical trials is documented. This information should be integrated into a process development report.

The development and implementation of the analytical methods used to support the release of a batch of APIs for clinical trials should be appropriately documented.

A system for retaining production and control records should be used. This system should ensure that records are retained for an appropriate length of time after the approval, termination, or discontinuation of an IND or NDA.

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GLOSSARY

The following terms and definitions are provided to assist the reader in using this guidance document. Unless otherwise stated, when the following definitions address APIs, the Agency intends to apply the same definitions to drug, veterinary, and biologic APIs.

Acceptance Criteria: The specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan that are necessary for making a decision to accept or reject a lot or batch of raw material, intermediate, packaging material, or active pharmaceutical ingredient. This term can also be applied to validation.

Act: The Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.).

Actual Yield: The quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular API or intermediate.

Active Pharmaceutical Ingredient (API): Any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body of humans or other animals. APIs include substances manufactured by processes such as (1) chemical synthesis; (2) fermentation; (3) recombinant DNA or other biotechnology methods; (4) isolation/recovery from natural sources; or (5) any combination of these processes.

Agency: The United States Food and Drug Administration (FDA).

Analytical Methods Validation: The process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications.

Batch: A specific quantity of an intermediate or API intended to have uniform character and quality, within specified limits, and produced according to a single manufacturing order during the same cycle of manufacture. A batch may also mean a specific quantity of material or API processed in one process or series of processes so that it could be expected to be homogenous.

Biologic Active Pharmaceutical Ingredient: A material originating from a biological manufacturing process intended to furnish pharmacological activity or other direct effect in the cure, treatment, or prevention of disease or conditions of human beings.

Biologic Product: Any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or conditions of human beings.

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a traceable standard over an appropriate range of measurements.

Chemical Reaction: A process that involves a chemical transformation of a starting material or intermediate to form a new compound (e.g., bond formation, oxidation, reduction).

Cleaning Agent: Any material used to clean process equipment, utensils, and storage vessels. These may include soaps, detergents, surfactants, alkalis, acids, or other materials, such as organic solvents, if the solvent is specifically used for cleaning and is not a solvent used in the next processing step.

Concurrent Validation: A subset of prospective validation in which API batches are released for distribution, based on extensive testing, before completion of process validation. Once data from additional batches produced under replicated conditions show uniformity, the process may be considered validated.

Containment: Achieving a level of control over a raw material, intermediate, or API that provides proper protection of these materials from external contamination and cross-contamination.

Contamination: The introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API (e.g., occurring during production, sampling, packaging or repackaging, storage or transport).

Continuous Production: A process in which a material is continuously produced in a step or series of steps. In a continuous process, the batches of raw materials and the process parameters can be statistically, but not absolutely, correlated to the material produced in a given period of time.

Critical Process Parameters: Process parameters that must be controlled within established operating ranges to ensure that the API or intermediate will meet specifications for quality and purity.

Critical Process Steps: Process steps that must be controlled within established operating ranges to ensure that the API or intermediate will meet specifications for quality and purity.

Cross-contamination: A contamination of a material or product with another material or product.

Development Report: A report that summarizes the major stages of API development from early stages through large-scale manufacturing.

Drug: As defined in Section 201(g)(1) of the Act means (a) articles that are recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to them; (b) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or other animals; and articles (other than food) intended to affect the structure or any function of the body of humans or other animals.

Drug Product: A finished dosage form, for example, a tablet, capsule or solution, that contains an active pharmaceutical ingredient, generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an API but is intended to be used as a placebo.

Enantiomers: Compounds with the same molecular formula as the API, which differ in the spatial arrangement of atoms within the molecule and are nonsuperimposable mirror images.

Expected Yield: The quantity of API or intermediate or the percentage of theoretical yield anticipated at any appropriate phase of production based on data from process development or process validation.

Expiry/Expiration Date: The date (usually placed on the containers/labels of an API) designating the time during which the API is expected to remain within established shelf-life specifications if stored under defined conditions and after which it should not be used**.**

Extraneous Substance: An impurity arising from any source extraneous to the manufacturing process.

Identified Impurity: An impurity for which a structural characterization has been achieved.

Impurity: Any component of an API that is not the entity defined as the API.

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

In-Process Controls: Testing and activities performed during production to monitor and, if necessary, adjust the process.

In-Process Material: Any material manufactured, blended, or derived by chemical reaction that is produced for, and used in, the preparation of an API.

Intermediate: A material produced during steps in the synthesis of an API that must undergo further molecular change or processing before it becomes an API.

Ligand: An agent with a strong affinity to a metal ion.

Lot: A batch, or a specific identified portion of a batch having uniform character and quality within specified limits. For an API produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified limits.

Lot Number (Control Number, or Batch Number): Any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of an API or other material can be determined.

Manufacture, Processing, Packing, or Holding: All operations used to manufacture an API to include packaging and labeling operations, testing, and quality control of an API.

Mother Liquor: The residual saturated liquid that remains after crystallization. A mother liquor may contain unrecovered or unreacted starting materials, intermediates, the API and/or impurities.

New Molecular Entity: The designated therapeutic moiety (API) in a dosage form that has not been approved for marketing in the United States (also referred to as a new chemical entity or new drug substance). It may be a complex, simple ester, or salt of a previously approved API.

Physical Manipulation: A process other than a chemical reaction that may change the purity or the physical properties of the material, including but not limited to crystallization, recrystallization, gel filtration, chromatography, milling, drying, or blending.

Pilot Scale: The manufacture of an API on a reduced scale by processes representative of and simulating those to be applied on a larger commercial manufacturing scale.

Polymorphism: The occurrence of different crystalline forms of the same API.

Potential Impurity: An impurity that, from theoretical considerations, may arise from or during manufacture. It may or may not actually appear in the API.

Primary Reference Standard: A particular portion, lot or batch of an API or intermediate that has been shown by an extensive set of analytical tests to be of the highest purity. This standard may be purchased from a recognized source or may be prepared by independent synthesis or by further purification of existing production material.

Process Validation: Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.

Prospective Validation: Establishing documented evidence that a system does what it purports to do prior to the commercial distribution of a new API or an existing API made by a new or modified process.

Purification Procedure: A process, such as crystallization, distillation, or chromatography, intended to improve the purity of an API or intermediate.

Qualification: The action of proving that any equipment or process works correctly and consistently and produces the expected results. Qualification is part of, but not limited to, a validation process, i.e., installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ).

Quality Assurance: The sum total of the organized activities performed with the intent to ensure that all APIs are of the quality required for their intended use.

Quality Control Unit: Any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

Quarantine: The status of materials isolated physically or by other effective means pending a decision on their subsequent use.

Range for Critical Process Parameter: The range for each process parameter generally developed on laboratory-, pilot-, or plant-scale batches that encompasses values that are capable of producing intermediates and APIs having acceptable quality attributes.

Raw material: Any ingredient intended for use in the production of APIs. These may include starting materials, process aids, solvents, and reagents.

Reagent: A substance, other than a starting material or solvent, that is used in the manufacture of an API or intermediate.

Recovery: Any treatment of materials by a process intended to make them suitable for further use.

Repeating a Chemical Reaction: Adding fresh reagents or solvents to unreacted or base material and repeating a chemical reaction from its beginning. This excludes those situations where a chemical reaction is continued or extended in the same vessel with the addition of more solvent, to ensure completion of a reaction or increase the yield and/or purity of the API (e.g., continuation of a hydrogenation step).

Reprocessing: Introducing an intermediate or API that does not conform to standards or specifications, back into the process and repeating one or more steps that are part of the established manufacturing process (e.g., recrystallization using the same solvent).

Retest Date: The date when the API should be re-examined to ensure that it is still suitable for use.

Retest Period: The period of time during which the API can be considered to remain within specifications, and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under defined conditions. After this period, the API should be retested for compliance with specifications before use.

Retrospective Validation: Establishing documented evidence that a system does what it purports to do based on a review and analysis of historic information. It is normally conducted on an API already being commercially distributed and is based on accumulated production, testing, and control data.

Reworking: Subjecting an intermediate or API that does not conform to standards or specifications, to one or more processing steps that are different from the established manufacturing process (e.g., recrystallizing with a different solvent).

Solvent: Any liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of an API or intermediate.

Starting Material: A material used in the synthesis of an API, which is incorporated as an element into the structure of an intermediate and/or of the API. Starting materials are normally commercially available and of defined chemical and physical properties and structure.
Theoretical Yield: The quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular API or intermediate, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

Toxic Impurity: Impurities having significant undesirable biological activity.

Unidentified Impurity: An impurity that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Validation Protocol: A written plan stating how validation will be conducted and identifying specific acceptance criteria. For example, the protocol for a typical manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling and test data to be collected, number of validation runs, and acceptable test results.

Working Standard: An API, intermediate or other substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference for routine laboratory analysis.