SECTION 1

GOOD MANUFACTURING PRACTICES (GMP) AND OTHER FDA GUIDELINES
1.1

GOOD MANUFACTURING PRACTICES (GMP) AND RELATED FDA GUIDELINES

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Pharmaceutical Manufacturing Handbook: Regulations and Quality, edited by Shayne Cox Gad
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1.1.1 FDA REGULATIONS: REAL AND IMAGINED

A regulation is a law. In the United States, all federal laws have been arranged or codified in a manner that makes it easier to find a specific law. The Code of Federal Regulations (CFR) is a compilation of all federal laws published in the Federal Register by the executive departments and agencies of the federal government. This code is divided into 50 titles which represent broad areas of federal regulation. Each title is further divided into chapters. The chapters are then subdivided into parts covering specific regulatory areas. Changes and additions are first published in the Federal Register. Both the coded law and the Federal Register must be used to determine the latest version of any rule. All food- and drug-related laws are contained in Title 21 of the CFR. Each title of the CFR is updated annually. Title 21 is updated as of April 1 of each year.

Because virtually all of the drug regulations are written to state what should be done but do not tell how to do it, the Food and Drug Administration (FDA) also publishes guidance documents. These documents are intended to provide precisely what the name implies—guidance. In this context, guidance documents are not law and do not bind the FDA or the public. Manufacturers are not required to use the techniques or approaches appearing in the guidance document. In fact, FDA representatives have repeatedly stated that the regulations were not written to suggest how something should be done in order to encourage innovation. While following the recommendations contained in the guidance documents will probably assure acceptance (agency philosophy and interpretation may have changed since the guidance document was published), other approaches are encouraged. No matter how they choose to proceed, manufacturers should be prepared to show that their methods achieve the desired results.

A method used by the FDA to “float” new ideas is to discuss them at industry gatherings such as FDA-sponsored seminars or meetings of industry groups such as the Pharmaceutical Manufacturers Association (PMA), the Parenteral Drug Association (PDA), and the International Society of Pharmaceutical Engineering (ISPE). Again, it must be remembered that while these comments reflect current FDA thinking, they are simply thoughts and recommendations. They are not law.

Several industry groups also publish comments, guidelines, and so on, that put forth current thinking of the group writing the document. These publications are interesting and often bring out valuable information. However, it is important to remember that these publications are not regulations or even official guidance documents. If a firm chooses to follow the recommendations of such documents, they are probably following good advice. However, since the advice comes from a nonofficial source, firms should still be prepared to defend their actions with good scientific reasoning.

1.1.2 21 CFR 210 AND 211: CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

Parts 210 and 211 of CFR Title 21 are the laws defining good manufacturing practices for finished pharmaceutical products. All manufacturers must follow these regulations in order to market their products in the United States. When a firm files an application to market a product in the United States through a New Drug Application (NDA), abbreviated NDA, (ANDA), Biological License Application (BLA),
or other product application, one of the last steps in approving the application is a preapproval inspection of the manufacturing facility. A major purpose of this inspection is to assure adherence to the GMP regulations. Preapproval inspections are a part of every application approval. Thus, if a firm has 10 applications pending, it should expect 10 inspections. The fact that the manufacturing facility has already been inspected will not alter the need for another inspection.

The FDA also has the right to visit and inspect any manufacturing facility that produces a product or products sold in the United States. Such inspections are unannounced. A manufacturer must admit an inspector when he or she appears at that facility and must do so without undue delay.

GMP requirements for manufacturers of pharmaceutical dosage forms are discussed below. This information should not be considered to be an exact statement of the law. We have attempted to show intent and, occasionally, add some comments that will clarify how that particular regulation is interpreted. For precise wording of a regulation, refer to the CFR and then check the Federal Register to determine if there have been any changes since the last update.

**General Provisions**

1. This section pertains to the manufacture of drug products for humans or animals.
2. These requirements will not be enforced for over-the-counter (OTC) drug products if the products and all their ingredients are ordinarily marketed and considered as human foods and which products may also fall within the legal definition of drugs by virtue of their intended use.

**Organization and Personnel**

1. Responsibilities of quality control unit
   (a) A quality control unit must be a part of the facility organization.
   (b) This unit must be given responsibility and authority to approve or reject all components, drug product containers, closures, process materials, packaging material, labeling, and drug products, and the authority to review production records.
   (c) Adequate laboratory facilities for testing and approval or rejection of the above listed materials must be available.
   (d) The quality control unit is responsible for approving or rejecting all procedures or specifications that impact on the identity, strength, quality, and purity of the drug product.
   (e) Responsibilities and procedures applicable to the quality control unit must be written and these procedures must be followed.
2. Personnel qualifications
   (a) Every person involved in the manufacture, processing, packing, or holding of a drug product must have education, training, and experience that enable that individual to perform their duties. Employees must be trained in the particular operations that they perform and in Current GMPs (CGMPs). The GMP training must be conducted by qualified individuals and with sufficient frequency to assure that workers remain familiar with the requirements applicable to them.
(b) Persons responsible for supervision must have the education, training, and experience to perform their assigned functions in such a manner as to assure that the drug product has the safety, identity, strength, quality, and potency that it is represented to possess.
(c) There must be an adequate number of qualified personnel to perform the needed tasks.

3. Personnel responsibilities
   (a) Personnel shall wear clean clothing appropriate for the duties they perform. Protective apparel must be worn as necessary.
   (b) Personnel shall practice good sanitation and health habits.
   (c) Only personnel authorized by supervisory personnel shall enter those areas designated as limited-access areas.
   (d) Any worker considered to have an apparent illness or open lesions that may adversely affect safety or quality of drug products shall be excluded from direct contact with product, components, or containers.

4. Consultants that advise on the manufacture, processing, packing, or holding of drug products must have sufficient education, training, and experience to advise on the subject for which they are retained. The manufacturer must maintain records of name, address, and qualifications of any consultants and the type of service they provide.

Buildings and Facilities

1. Design and construction features
   (a) Buildings should be of suitable size, construction location to facilitate cleaning, maintenance, and proper operations.
   (b) Space should be adequate for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers and closures, labeling, in-process materials, or drug products and to prevent contamination.
   (c) The movement of components and product through the building must be designed to prevent contamination.
   (d) Operations should be performed within specifically defined areas having adequate control systems to prevent contamination or mix-ups during each of the following procedures:
      (i) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, and release for manufacturing or packaging.
      (ii) Holding rejected materials listed in (a) above.
      (iii) Storage of released components, drug product containers, closures, and labeling.
      (iv) Storage of in-process materials.
      (v) Manufacturing and processing operations.
      (vi) Packaging and labeling operations.
      (vii) Quarantine storage before release of drug products.
      (viii) Storage of drug products after release.
      (ix) Control and laboratory operations.
(x) Aseptic processing, which includes:

(1) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable.

(2) Temperature and humidity controls.

(3) An air supply filtered through High-Efficiency Particulate Air (HEPA) filters under positive pressure regardless of whether flow is laminar or nonlaminar.

(4) A system for monitoring environmental conditions.

(5) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

(6) A system for maintaining any equipment used to control the aseptic conditions.

(e) Operations relating to the manufacture, processing, and packing of penicillin must be performed in facilities separate from those used for other drug products for humans. Note: For all purposes of these GMP regulations, the FDA considers cephalosporins to be penicillin.

2. Adequate lighting should be provided in all areas.

3. Heating, ventilation, and air conditioning (HVAC)

(a) Adequate ventilation is required in all areas.

(b) Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature must be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

(c) When appropriate, air supplied to production areas should be filtered to avoid any possibility of contamination or cross-contamination.

(d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for humans.

4. Plumbing

(a) Potable water should be supplied in a continuous positive-pressure system free from defects that could contribute to contamination of any drug product.

(b) Potable water must meet the standards prescribed in the Environmental Protection Agency (EPA) Primary Drinking Water Regulations defined in 40 CFR Part 141.

(c) Drainage must be of adequate size. Where connected directly to a sewer, an air break or other suitable mechanical device must be provided to prevent back-siphonage.

5. Sewage, trash, and other refuse in and from the building and immediate premises must be disposed of in a safe and sanitary manner.

6. Adequate washing facilities should be provided. This is to include hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to all work areas.

7. Sanitation

(a) Any building used for manufacture, processing, packing, or holding of a drug product should be maintained in a clean and sanitary condition. Such buildings should be free of infestation by rodents, birds, insects, and other vermin.

(b) Trash and organic waste matter should be held and disposed of in a timely and sanitary manner.
(c) Written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities are required. Such procedures must be followed.

(d) Written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents are required and must be followed. These written procedures should be designed to prevent the contamination of equipment, components, product containers, closures, packaging, labeling materials, or drug products. Agent may not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135).

(e) All sanitation procedures apply equally to contractors or temporary employees as to regular employees.

8. All buildings used for GMP-related purposes must be maintained in a good state of repair.

**Equipment**

1. Equipment should be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for cleaning and maintenance.

2. Equipment construction
   (a) Equipment should be constructed so that surfaces that contact components, in-process materials, or drug products should not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond official or other established requirements.
   (b) Any substance required for operation such as lubricants or coolants shall not come into contact with drug products, containers, and so on, so as to alter the safety, identity, strength, quality, or purity of the drug product beyond established requirements.

3. Equipment cleaning and maintenance
   (a) Equipment and utensils should be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the drug product beyond the official requirements.
   (b) Written procedures must be established and followed for cleaning and maintenance of equipment and utensils used in the processing of a drug product. These procedures must include but are not limited to the following:
      (i) Assignment of responsibility for cleaning and maintaining equipment.
      (ii) Maintenance and cleaning schedules, including sanitizing schedules if appropriate.
      (iii) A sufficiently detailed description of the methods, equipment, and materials used in cleaning and maintenance operations and the methods of disassembling and reassembling equipment as a part of cleaning and maintenance.
      (iv) Removal or obliteration of previous batch identification.
      (v) Protection of clean equipment from contamination prior to use.
      (vi) Inspection of equipment for cleanliness immediately before use.
(vii) Records should be kept of maintenance, cleaning, sanitizing, and inspection of all processing equipment.

4. Automatic, mechanical, and electronic equipment
   (a) All such equipment, including computers or related systems that will perform a function to be used in any GMP-related activity, must be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records must be maintained for all such activities.
   (b) Appropriate controls should be exercised to assure that changes in master production and control records or other similar records are made only by authorized personnel. Input to and output from such systems should be checked for accuracy.

A backup file of data entered into a computer-related system must be maintained except where certain data such as calculations performed in connection with laboratory analysis are eliminated by computerization or other automated processes. In this situation, a written record of the program should be maintained along with validation data.

5. Filters for liquid filtration used as a part of the manufacture, processing, or packing of injectable drug products intended for human use must not release fibers into such products. Fiber-releasing filters may not be used unless it is not possible to manufacture the product without the use of such a filter. In this situation, an additional non-fiber-releasing filter of 0.22 μm maximum must be used after the fiber-releasing filtration. Use of an asbestos-containing filter is permissible only upon submission of proof to the appropriate FDA bureau that use of a non-fiber-releasing filter will compromise the safety or effectiveness of the drug product.

**Control of Components and Drug Product Containers and Closures**

1. General requirements
   (a) There must be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of product components, containers, and closures. Of course, all such procedures must be followed. It is quite common and even more embarrassing to be cited for not following your own written procedures. *Note:* For the rest of this discussion, the term *components* will mean product ingredients, containers, closures, and so on.
   (b) All components listed above must be handled and stored in a manner that will prevent contamination.
   (c) Bagged or boxed components should be stored off the floor. Spacing should allow cleaning and inspection.
   (d) Every container of components must be identified with a distinctive code or lot number for each receipt of that product. Even if the next receipt is the same vendor lot number, it must be a new identifying number by the pharmaceutical manufacturer. Each lot must be appropriately identified as to its status (quarantined, approved, or rejected).
2. Receipt and storage of untested components
   (a) Upon receipt each container of components must be visually examined for appropriate labeling and any damage or contamination to the component container.
   (b) Components must be stored under quarantine until they have been tested as appropriate and released for use.

3. Testing and approval or rejection of components
   (a) Each lot of components shall be withheld from use until it has been sampled, tested, and released by the quality control unit.
   (b) Representative samples must be taken from every receipt of every component. The number or amount of component to be sampled should be based on component appearance, statistical confidence levels, the past history of the supplier, and the quantity needed to analyze and reserve samples if required.
   (c) Sampling procedures
      (i) The component containers should be cleaned where necessary.
      (ii) The containers should be opened, sampled, and resealed in a manner designed to prevent contamination of the sample and remaining contents of the container.
      (iii) If appropriate, sterile equipment and aseptic sampling techniques should be used.
      (iv) Where sampling is done from various parts of a container, samples should not be composited for testing.
      (v) Containers from which samples have been taken must be marked to show that samples have been removed.
   (d) Examination and testing of samples
      (i) At least one test should be conducted on each lot of component drug product to verify identity.
      (ii) Each component must be tested for conformity with all appropriate written specifications for purity, strength, and quality if an ingredient or for conformity with written specifications for containers or closures.
      (iii) In lieu of the above testing by the manufacturer, a report of analysis may be accepted from the supplier provided that at least one specific identity test is conducted on the component by the manufacturer and provided that the manufacturer has established the reliability of the supplier’s analyses through appropriate validation.
      (iv) When appropriate, components should be examined microscopically.
      (v) Each lot of a component that is liable to contamination with dirt, insect infestation, or other extraneous adulterant should be examined against established specifications for such contamination.
      (vi) Each lot of a component that is subject to microbial contamination that is contrary to its intended use should be subjected to microbiological tests before use.
   (e) If a lot of components meets the written specifications, it may be approved and released for use. Any lot of such material that does not meet such specifications must be rejected.

4. Use of approved components (including drug product containers and closures) must be rotated to assure that the oldest approved stock is used first.
5. Components must be retested and/or reexamined after storage for a long period of time or after exposure to the atmosphere, heat, or other condition that might adversely affect the component.

6. Rejected components should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing.

7. Containers and closures
   (a) Containers and closures must not be reactive, additive, or absorbent so as to alter the drug beyond established acceptance criteria.
   (b) Container closure systems must provide adequate protection against foreseeable external factors in storage that can cause deterioration or contamination of the product.
   (c) Containers and closures should be clean and, if necessary, sterile and processed to remove pyrogens.
   (d) Standards or specification, methods of testing, and, if appropriate, sterilization and depyrogenation must be written and followed.

**Production and Process Controls**

1. Written procedures and procedure deviations
   (a) Written procedures for production and process control must be written and followed. These procedures should be designed to assure that the drug products have the identity, strength, quality, and purity they are represented to possess. These procedures must include all requirements given below and must be drafted, reviewed, and approved by the affected organizational units and reviewed and approved by the quality control unit.
   (b) When following the above identified procedures, all actions must be documented at the time of performance. Any deviations from the written procedure must be recorded and justified.

2. Charge-in of components—Written production and control procedures must include the following, which are designed to assure that the drug products produced meet all specifications and standards.
   (a) The batch must be formulated with the intent to provide not less than 100% of the labeled amount of active ingredient.
   (b) Components used must be weighed, measured, or subdivided appropriately. If a component is removed from its original container and placed in another, the new container should be identified with the following information:
      (i) Component name and/or item code.
      (ii) Receiving or control number.
      (iii) Weight or measure of material in the new container.
      (iv) Batch or lot number for which the component was dispensed, including its product name, strength, and lot number.
   (c) Weighing, measuring, or subdividing operations for all components must be adequately supervised. Each container of component dispensed to manufacturing must be examined by a second person to assure that:
      (i) The component was released by the quality control unit.
      (ii) The weight or measure is correct as stated in the batch production records.
(iii) The containers are properly identified and contain the quantity stated on the label.

(d) Addition of each component must be performed by one person and verified by a second person.

3. Actual yield and percentage of theoretical yield should be determined at the completion of each appropriate phase of manufacturing, processing, packaging, or holding. These calculations should be performed by one person and independently verified by a second individual.

4. Equipment identification
   (a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product must be properly identified at all times to indicate their contents and the phase of processing of the batch.
   (b) Major equipment should be identified by a distinctive identification that shall be recorded in the batch production record to indicate the specific equipment used. In cases where only one of a particular type of equipment exists in a given manufacturing facility, the name of the equipment may be used instead of creating a distinctive identification.

5. Sampling and testing of in-process materials and drug products
   (a) To assure batch uniformity and integrity, it is necessary to write and follow procedures that describe the in-process controls and tests or examinations that will be conducted on samples taken according to procedure. Procedures should be written to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the product being manufactured. These control procedures should include but are not limited to the following:
      (i) Tablet or capsule weight variation.
      (ii) Disintegration time.
      (iii) Adequacy of mixing or blending to assure uniformity and homogeneity.
      (iv) Dissolution time and rate.
      (v) Clarity of solutions.
      (vi) pH of solutions.
   (b) In-process specifications for all characteristics must be consistent with the drug product final specifications and must be developed from previous acceptable product average and process variability data.
   (c) In-process materials should be tested for identity, strength, quality, and purity as appropriate. As a part of the production process, they must be approved for continued use or rejected by the quality control unit before production continues.
   (d) Rejected in-process materials must be identified and controlled under a quarantine system designed to prevent their use in manufacturing operations for which they have been found to be unsuitable.

6. When appropriate, time limits should be established for the completion of each phase of production. The purpose of this is to assure the quality of the drug product. Deviation from the established time limits may be acceptable if this deviation does not compromise the quality of the product. Any deviation must be documented, including the justification for such deviation.
7. Control of microbial contamination
   (a) To prevent the growth of objectionable microorganisms in products not required to be sterile, appropriate written procedures designed to prevent such growth should be written and followed.
   (b) If sterilization is a part of any procedure described in (a) above, this procedure must be validated.

8. Reprocessing
   (a) Written procedures describing any system used to reprocess batches that do not conform to the established standards must be written and followed.
   (b) Reprocessing must not be performed without the review and approval of the quality control unit.

Packaging and Labeling Control

1. Materials examination and usage criteria
   (a) Written procedures describing in detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials must be developed, approved, and followed. These materials must be representatively sampled, examined, or tested on receipt and accepted by the quality control unit before use.
   (b) Any materials that do not fully meet acceptance criteria must be rejected to prevent their use.
   (c) Records of each receipt of each different label and packaging material must be maintained indicating receipt, examination or testing, and whether accepted or rejected.
   (d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents must be stored separately with suitable identification. Access to the storage area must be limited to authorized personnel.
   (e) Obsolete and outdated labels, labeling, and other packaging materials must be quarantined and destroyed.
   (f) The use of gang-printed labels for different drug products or different strengths or different net contents is prohibited. The only exception to this rule is if labels from gang-printed sheets are adequately differentiated by size, shape, or color that will prevent mixing of labels.
   (g) If cut labeling is used, packaging and labeling operations must include one or more of the following special control procedures:
      (i) Dedication of a labeling and packaging line to each different strength of each different drug product.
      (ii) Use of appropriate electronic or electromechanical equipment to conduct a 100% examination for correct labeling during or after completion of the finishing operation.
      (iii) Use of visual inspection to conduct a 100% examination for correct labeling. If visual inspection is used, the inspection should be performed by one person and independently verified by a second individual.
   (h) Printing devices on or associated with the manufacturing line used to imprint labeling upon the drug product unit label or case must be monitored to assure
that the printing conforms to the print specified in the batch production record.

2. Issuance of labeling
   (a) Strict control should be exercised over the issuance of labeling for use in drug product labeling operations.
   (b) Labeling materials issued for a batch must be carefully examined for identity and conformity to the labeling specified in the batch production record.
   (c) Procedures should be written and followed for reconciliation of the quantities of labeling issued, used, destroyed, and returned. Procedures should require evaluation of discrepancies found between the number of packages finished and the amount of labeling issued if discrepancies outside narrow preset limits occur. Limits should be established on the basis of historical operating data. Labeling reconciliation is waived for either cut or roll labeling if a 100% examination for correct labeling is performed.
   (d) All excess labeling bearing a lot or control number must be destroyed.
   (e) Returned labeling should be maintained and stored in a manner to prevent mix-ups.
   (f) Written procedures should describe the control procedures used for the issuance of labeling.

3. There must be written procedures designed to assure that correct labels, labeling, and packaging materials are used. These procedures should incorporate the following features:
   (a) Prevention of mix-ups and cross-contamination by physical or spatial separation of operations on other drug products.
   (b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations. Such procedures should be designed to prevent mislabeling individual containers, lots, or portions of lots. It is not necessary to apply identification to each individual container, but the procedure should be adequate to determine the name, strength, quantity of contents, and lot or control number of each container.
   (c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.
   (d) Examination of packaging and labeling materials for suitability and correctness before issuing for use and before packaging operations. These examinations must be documented in the batch production record.
   (e) Inspection of the packaging and labeling facility immediately before use to assure that all drug products and labeling materials from the previous operation have been removed. Inspection results must be documented in the batch production record.

4. Tamper-evident packaging requirements for OTC human drug products
   (a) An OTC product (with the exception of a dermatological, dentifrice, insulin, or lozenge product) intended for retail sale is considered adulterated or misbranded or both if it is not packaged in a tamper-resistant package.
   (b) Requirements for a tamper-evident package
      (i) With the exceptions listed above, all OTC products must be packaged in a tamper-evident package if the product is accessible to the public while being held for sale. A tamper-evident package must have
one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred: A tamper-evident package may involve an immediate container and closure system or a secondary container or carton system or a combination of systems intended to provide a visual indication of package integrity. The tamper-evident feature must be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

(ii) In addition to the tamper-evident packaging feature described above, any two-piece hard gelatin capsule covered by this regulation must be produced using an acceptable tamper-evident technology.

(c) Labeling

(i) In order to alert consumers to the specific tamper-evident features used, each retained package of an OTC drug product covered by this regulation is required to bear a statement that:

(1) Identifies all tamper-evident features and any capsule-sealing technologies.

(2) Is prominently placed on the package.

(3) Is so placed that it will be unaffected if the tamper-evident feature of the package is breached or missing.

(ii) If the tamper-evident feature chosen to meet the requirement uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say For your protection, this bottle has an imprinted seal around the neck.

(d) A manufacturer or packer may request an exemption from the tamper-evident requirement. A request for exemption is required to be submitted in the form of a petition and should be clearly identified on the envelope as a “Request for Exemption from the Tamper-Evident Packaging Rule.” This petition is required to contain the following:

(i) The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class and a list of products within that class.

(ii) The reasons that the drug product’s compliance with the tamper-evident packaging and labeling requirements is unnecessary or cannot be achieved.

(iii) A description of alternative steps that are available or that the petitioner has already taken to reduce the likelihood that the product or drug class will be the subject of malicious adulteration.

(iv) Other information justifying an exemption.

(e) Holders of approved new drug applications for OTC drug products are required to provide the FDA with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labeling required by the regulation may be made before FDA approval. Manufacturing changes by which capsules are to be sealed require prior FDA approval.

(f) This section does not affect any requirements for “special packaging” as required under the Poison Prevention Packaging Act of 1970.
5. Drug product inspection
   (a) Packaged and labeled products must be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.
   (b) A representative sample of units should be collected at the completion of finishing operations and should be visually examined for correct labeling.
   (c) Results of these examinations must be recorded in the batch production records.

6. Expiration dating
   (a) All packaged drug products must carry an expiration date that has been determined from appropriate stability testing.
   (b) Expiration dates must be related to the recommended storage conditions stated on the label as determined by stability studies.
   (c) If the drug product is to be reconstituted at the time of dispensing, its label must carry expiration information for both the reconstituted and unreconstituted forms.
   (d) Expiration dates must appear on labeling in accordance with the requirements stated elsewhere in this regulation.
   (e) Homeopathic drug products are exempt from the requirements of this section.
   (f) Allergenic extracts that are labeled “No U.S. Standard of Potency” are exempt.
   (g) New drug products for investigational use are exempt provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. If new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling must bear expiration information for the reconstituted product.
   (h) Pending consideration of a proposed exemption published in the Federal Register, September 29, 1978, the requirements in this section will not be enforced for human drug products if their labeling does not bear dosage limitations and they are stable at least three years as supported by stability data.

Holding and Distribution

1. Warehousing procedures
   (a) Written procedures describing the warehousing of drug products must be written and followed. These procedures should include:
      (i) Quarantine of drug products before release by the quality control unit.
      (ii) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the quality of the drug products is not affected.

2. Distribution procedures
   (a) Written procedures concerning the distribution of drug products must be established and followed. These procedures should include:
      (i) A procedure that assures the distribution of the oldest approved stock first. Deviation from this procedure is acceptable if it is temporary and appropriate.
(ii) A system for documenting distribution so that distribution of each lot of drug product can be readily determined to facilitate its recall if required.

**Laboratory Controls**

1. General requirements
   (a) The establishment of any specifications, standards, sampling plans, test processes, or other laboratory control mechanism required by this part of the regulation, including any changes to the above must be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. All actions must be documented at the time of performance and any deviation must be recorded and justified.
   (b) Laboratory controls must include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that all materials conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls should include:
      (i) Determination of conformance to written specifications for the acceptance of each lot within each shipment of raw materials. The specifications should include a description of the sampling and testing procedures used. Samples must be representative and adequately identified. These procedures must also require appropriate retesting of any material that is subject to deterioration.
      (ii) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials.
      (iii) The calibration of instruments, apparatus, gauges, and recording devices at specified intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event that the limits are not met. Any such devices that do not meet the established specifications must not be used.

2. Testing and release for distribution
   (a) Laboratory testing of each lot of drug product must be conducted to establish conformance to final specifications for the product. Testing must include identity and strength of each active ingredient. Where sterility and/or pyrogen testing are required on short-lived radiopharmaceuticals, batches may be released prior to completion of this testing provided that such testing is completed as soon as possible.
   (b) Each batch of product required to be free of objectionable microorganisms must be tested appropriately.
   (c) All sampling and testing plans must be described in written procedures that include the method of sampling and the number of units to be tested.
   (d) Acceptance criteria for the sampling and testing conducted by the quality control unit must be adequate to assure that the batch being tested meets all specifications. Appropriate statistical quality control criteria should be used. The statistical quality control criteria must include acceptance levels and/or rejection levels.
(e) The accuracy, sensitivity, specificity, and reproducibility of test methods used must be established and documented. Validation and documentation must be accomplished in accordance with this regulation.

(f) Drug products failing to meet established standards or specifications and any relevant quality control criteria must be rejected. Reprocessing may be performed, however, prior to acceptance and use, and reprocessed material must meet all standards, specifications, and other relevant criteria.

3. Stability testing
   (a) There must be a written testing program designed to assess the stability characteristics of every drug product. The results of such testing must be used to determine appropriate storage conditions and expiration dates. The written program must include:
      (i) Sample size and test intervals based on statistical criteria for each attribute examined.
      (ii) Storage conditions for sampled retained for testing.
      (iii) Reliable, meaningful and specific test methods.
      (iv) Testing of the product in the same container-closure system as the one in which the product is to be marketed.
      (v) Testing of drug products for reconstitution at the time of dispensing as well as after they are reconstituted.

   (b) An adequate number of batches of each drug product must be tested to determine appropriate expiration date. A record of such data must be maintained. Accelerated studies, combined with basic stability information on the components and drug product in its container-closure system may be used to project a tentative expiration date that is beyond the date supported by shelf life studies. However, there must be stability studies conducted including drug product testing at appropriate intervals until the tentative expiration date is verified.

   (c) The requirements for homeopathic drug products are as follows:
      (i) There must be a written assessment of stability based on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.
      (ii) Evaluation of stability must be based on the same container-closure system as the one in which the drug product is to be marketed.

   (d) Allergenic extracts that are labeled “No U.S. Standard of Potency” are exempt from the requirements of this section.

4. Special testing requirements
   (a) For each batch of drug product claimed to be sterile and/or pyrogen free, there must be appropriate laboratory testing to establish conformance to this claim. The test procedures must be in writing and must be followed.

   (b) For each batch of ophthalmic ointment, there must be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures must be in writing and must be followed.

   (c) For each batch of controlled-release dosage form, there must be appropriate laboratory testing to determine conformance to the specifications for the rate
of release of each active ingredient. The test procedures must be in writing and must be followed.

5. Reserve samples

(a) An identified reserve sample that is representative of each lot or of each shipment of each active ingredient must be retained. This reserve sample should contain at least twice the quantity needed for all tests required to determine whether the active ingredient meets its established specifications with the exception of sterility and pyrogen testing. The required retention time is as follows:

(i) For an active ingredient in a drug product other than those described in paragraphs (b) and (c) below, the reserve sample must be retained for one year after the expiration date of the last lot of drug product containing that lot of active ingredient.

(b) For an active ingredient in a radioactive drug product except for nonradioactive reagent kits, the reserve sample must be retained for:

(i) Three months after the expiration date of the last lot of the drug product containing that lot of active ingredient if the expiration dating period of the drug product is 30 days or less.

(ii) Six months after the expiration date of the last lot of the drug product containing that lot of active ingredient if the expiration dating period of the drug product is more than 30 days.

(c) For an active ingredient in an OTC drug product that is exempt from bearing an expiration date, the reserve sample must be retained for three years after distribution of the last lot of drug product containing that lot of active ingredient.

(d) A properly identified reserve sample that is representative of each batch of drug product must be retained and stored under conditions consistent with the product labeling. The reserve sample must be stored in the same immediate container closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity needed to perform all the required tests except those for sterility and pyrogens. Reserve samples from representative sample lots or batches selected by acceptable statistical procedures must be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration must be investigated. The results of the examination must be recorded and maintained with stability data concerning that drug product. Retention times are as follows:

(i) For a drug product other than the exceptions noted above, the reserve sample must be retained for one year after the expiration date of the drug product.

(ii) For a radioactive drug product, except for nonradioactive reagent kits, the retention sample must be retained for:

(1) three months after the expiration date of the drug product if the expiration date is 30 days or less or

(2) six months after the expiration date of the drug product if the expiration date is more than 30 days.
(iii) For an OTC drug product that is exempt from bearing an expiration date, the reserve sample must be retained for three years after the batch of drug product is fully distributed.

6. Animals used in testing components, in-process materials, or drug products for compliance with established specifications must be maintained and controlled in a manner that assures their suitability for their intended use. They must be identified and adequate records must be maintained showing the history of their use.

7. If a reasonable possibility exists that a nonpenicillin drug product has been exposed to cross-contamination with penicillin, the nonpenicillin drug product must be tested for the presence of penicillin. The drug product may not be marketed if a detectable level of penicillin is found when tested according to procedures specified in “Procedures for Detecting and Measuring Penicillin contamination in Drugs” which is incorporated in the regulation by reference.

Records and Reports

1. General Requirements
   (a) Any production, control, or distribution record that is associated with a batch of a drug must be retained for at least one year after the expiration date of the batch OR, for OTC drug products that do not have expiration dates, three years after complete distribution of the batch.
   (b) Records must be retained for all components, containers, closures, and labeling for the same time periods shown in (a) above.
   (c) All retained records or copies of these records must be readily available for authorized inspection at any time in the required retention period. Records must be available for inspection where the activities described therein occurred. Photocopying or similar reproduction by investigators must be permitted.
   (d) Retained records may be original records or true copies such as photocopies, microfilm, microfiche, or other accurate reproduction of the original.
   (e) Written records that must be retained must be maintained so that data contained therein can be used for evaluating the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Such reviews should be conducted at least annually. Written procedures must be established and followed for these evaluations and must include provisions for:
      (i) A review of a representative number of batches, whether approved or rejected, and records associated with the batch.
      (ii) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under Section 211.192 of the GMP regulations for each drug product.
   (f) Procedures must be established to assure that the responsible officials of the firm are notified in writing of any investigations conducted under Sections 211.198, 211.204, or 211.208 of any recalls, reports of inspectional observations issued by the FDA, or any regulatory actions relating to GMP brought by the FDA.

2. A written record of major equipment cleaning, maintenance (except routine maintenance), and use must be included in individual equipment logs that show
the date, time, product, and lot number of each batch processed. The persons performing and double checking the cleaning and maintenance should date and sign or initial the log indicating that the work was performed. Entries in the log must be in chronological order.

3. Component, drug product container, closure, and labeling records must include the following:
   (a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling. Also required are the identity of the supplier, the supplier’s lot number(s), the receiving code, the date of receipt, and name and location of the prime manufacturer if different from the supplier.
   (b) The results of any test or examination performed and any conclusions derived from these results.
   (c) An individual inventory record of each component and a reconciliation of the use of each lot of such component. The inventory record must contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component.
   (d) Documentation of the examination and review of labels and labeling for conformance with established specifications.
   (e) The disposition of rejected materials.

4. Master production and control records
   Batch production and control records should be prepared for each batch of drug product produced and must include complete information about the production and control of that batch. These records must include:
   (a) A full and complete reproduction of the appropriate master production or control record. The copy must be checked for accuracy, dated, and signed.
   (b) Documentation that each significant step in the manufacture, processing, packaging, and holding of the batch was accomplished as prescribed, including:
      (i) Dates.
      (ii) Identity of individual major equipment used. This includes packaging lines.
      (iii) Complete and specific identification of each batch of component or in-process material used.
      (iv) Weight and measures of components used in the course of processing.
      (v) In-process and laboratory control results.
      (vi) Inspection of the packaging and labeling area before and after use.
      (vii) Documentation of the actual yield and the percentage of theoretical yield that this represents at critical stages of processing.
      (viii) Complete labeling control records, including specimens or copies of all labeling used.
      (ix) A description of drug product containers and closures.
      (x) Any sampling performed.
      (xi) Identification of the persons performing and directly supervising or checking significant steps in the operation.
      (xii) Any investigations conducted.
      (xiii) Results of examinations made.
5. All drug product production and control records, including those for packaging and labeling, must be reviewed and approved by the quality control unit to determine compliance with all established written procedures before a batch is released or distributed. Any unexplained discrepancy or the failure of a batch or any of its components to meet any of the established specifications must be thoroughly investigated. The investigation must be extended to other batches of the same drug product and other drug products that may have been associated with the specific fault or discrepancy. A written record of the investigation must be made and include the conclusions and any required follow-up.

6. Laboratory records

(a) Laboratory records must include complete data derived from all tests needed to assure compliance with established specifications and standards. This includes examinations and assays as follows:

(i) A description of the sample received for testing with identification of source. For example, location where the sample was obtained, quantity, lot number or other distinctive code, date the sample was taken, and the date that it was received for testing.

(ii) A statement of each method used in the testing of the sample. The statement must indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method used is in the current revision of the U.S. Pharmacopeia (USP), National Formulary (NF), or other recognized standard reference or if it is detailed in an approved NDA, this statement will not be required.)

(iii) A statement of the weight or measure of sample used for each test.

(iv) A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation properly identified to the specific component and lot tested.

(v) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.

(vi) A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component tested.

(vii) The initials or signature of the person who performed each test and the date the tests were performed.

(viii) The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

(b) Complete records must be maintained of any modification of an established method employed in testing. These records must include the reason for the modification and verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

(c) Complete records must be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

(d) Complete records must be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices.
(e) Complete records must be maintained of all stability testing performed in accordance with Section 211.166 of the regulation.

7. Distribution records must contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.

8. Complaint files
   (a) Written procedures describing the handling of all written and oral complaints regarding a drug product must be established and followed. These procedures must include provisions for review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of its specifications and a determination as to the need for an investigation. These procedures must include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the FDA.
   (b) A written record of each complaint must be maintained in a file designated for product complaints. The file may be maintained at another facility if the written records of such files are readily available for inspection at that other facility. Written reports involving a drug product must be maintained until at least one year after the expiration date of the drug product or one year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption, such written records must be maintained for three years after distribution of the drug product.
      (i) The written record must include the following information where known: the name and strength of the drug product, lot number, name of complainant, nature or complaint, and reply to the complainant.
      (ii) Where an investigation is conducted, the written record must include the findings of the investigation and follow-up. The record or a copy of the record of investigation must be maintained at the location where the investigation occurred.
      (iii) Where an investigation is not conducted, the written record must include the reason that an investigation was not considered to be necessary and the name of the responsible person making the determination.

Returned and Salvaged Drug Products

1. Returned drug products—Returned drug products must be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during the return or the condition of the drug product, its container, carton, or labeling is a result of storage or shipping casts doubt on the safety, identity, strength, quality, or purity of the drug product, the returned drug product must be destroyed unless examination testing or other investigation proves the drug product meets appropriate standards. Records of returned drug products must be maintained and must include the name and label potency of the drug
product dosage lot number, reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned product. If the reason for a drug product being returned implicates associated batches, an investigation must be conducted. Procedures for the holding, testing, and reprocessing of returned drug products must be in writing and must be followed.

2. Drug product salvaging—Drug products that have been subjected to improper storage conditions, including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures, must not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection of the premises that the drug products and associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations are acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition must be maintained for drug products subject to this section.

1.1.3 GUIDANCE FOR INDUSTRY: QUALITY SYSTEMS APPROACH TO PHARMACEUTICAL CURRENT GOOD MANUFACTURING PRACTICE REGULATIONS

This guidance document was written by the FDA to help manufacturers implement what they consider to be modern quality systems and risk management approaches that will meet the requirements of the FDA's GMP regulations. The guidance describes what the FDA considers a comprehensive quality systems (QS) model. It also explains how manufacturers can be in full compliance with the GMP regulations by implementing such quality systems. The FDA does not intend this guidance to place new expectations on manufacturers nor does this replace the GMPs.

As is true with all guidance documents, this document does not establish legally enforceable responsibilities, but rather it describes the FDA's current thinking. Thus, this guidance should be viewed as a set of recommendations unless a regulation is cited.

The objective of this guidance is to describe a quality systems model and demonstrate how and where the elements of this model can fit within the requirements of the CGMP regulations. The philosophy being put forward is that quality should be built into the product, and testing alone cannot be relied on to ensure product quality.

1.1.3.1 CGMPs and the Concepts of Modern Quality Systems

The FDA believes that several key concepts are critical for any discussion of modern quality systems. The following concepts are used throughout this guidance as they relate to the manufacture of pharmaceutical dosage forms:
Quality For the purposes of this guidance, the phrase achieving quality means achieving the identity, strength, purity, and other quality characteristics designed to ensure safety and effectiveness.

Quality by Design and Product Development This means designing and developing a product and its associated manufacturing processes that will be used to ensure that the product consistently attains a predefined quality at the end of the manufacturing process.

Quality Risk Management This component of a quality systems framework can help guide the setting of specifications and process parameters for dosage form manufacturing, assess and mitigate the risk of changing a process or specification, and determine the extent of discrepancy investigations and corrective actions.

Corrective and Preventative Action (CAPA) This is a regulatory concept that focuses on investigating, understanding, and correcting discrepancies while attempting to prevent their recurrence. This model separates CAPA into three separate concepts:
- Remedial corrections of an identified problem
- Root cause analysis with corrective action to help understand the cause of the deviation and prevent recurrence of a similar problem
- Preventative action to prevent recurrence of similar problems

Change Control This process focuses on managing change to prevent unintended consequences.

Quality Unit While the GMPs refer to a quality unit, current industry practice is to divide the responsibilities of this unit between two groups:
- Quality control (QC) usually involves (a) assessing the suitability of incoming components and the finished products, (b) evaluating the performance of the manufacturing process, and (c) determining the acceptability of each batch for release and distribution
- Quality assurance (QA) involves (a) review and approval of all procedures related to manufacturing and maintenance, (b) review of records, and (c) auditing and performing/evaluating trend analyses.

Six-System Inspection Model The FDA’s instruction manual for its investigators is a systems-based approach to inspection consistent with this guidance. The FDA defines six interlocked systems: (1) the quality system which encompasses all the other systems, (2) a materials system, (3) a production system, (4) a packaging and labeling system, (5) a facilities and equipment system, and (6) a laboratory controls system. The agency believes that use of this overall system approach will help firms achieve better control.

1.1.3.2 Quality Systems Model

This section was written to describe a model for use in pharmaceutical manufacturing that can supply the controls to consistently produce a product of acceptable quality. The model is described by four major factors:
Management Responsibilities
The FDA feels that a robust quality system model calls for management to play a key role in the design, implementation, and management of the quality system.

Resources
Sufficient resources should be provided to create a robust quality system that complies with the GMP regulations. Senior management or a designee should be responsible for providing adequate resources.

Facilities and Equipment
The technical experts who have an understanding of pharmaceutical science, risk factors, and manufacturing processes related to the product are responsible for defining specific facility and equipment requirements. The equipment must be qualified, calibrated, cleaned, and maintained to prevent contamination and product mix-ups. It is important to remember that the GMPs place as much emphasis on process equipment as on testing equipment while most quality systems focus only on testing equipment.

Control Outsourced Operations
Quality systems call for contracts with outside suppliers that clearly describe the materials or service, quality specification responsibilities, and communication mechanisms.

Manufacturing
There is an overlap between the elements of a quality system and the GMP regulation requirements for manufacturing operations. One should always remember that the FDA’s enforcement programs and inspectional coverage are based on the GMPs. The FDA feels that the following factors are essential in a manufacturing quality system:
1. Design, develop, and document product and processes
2. Examine inputs
3. Perform and monitor operations
4. Address nonconformities

Evaluation Activities
This includes the following activities:
1. Analyze data for trends
2. Conduct internal audits
3. Quality risk management
4. Corrective action
5. Preventative action
6. Promote improvements

1.1.4 GUIDANCE FOR INDUSTRY: PAT—FRAMEWORK FOR INNOVATIVE PHARMACEUTICAL DEVELOPMENT, MANUFACTURING, AND QUALITY ASSURANCE

This guidance is intended to describe a regulatory framework that the FDA chooses to call process analytical technology, or PAT. It is the FDA’s hope that this will
encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance. The FDA intended this guidance for a broad audience in different organizational units. To a large extent, the guidance discusses principles with the goal of highlighting opportunities and developing regulatory processes that encourage innovation.

Conventional pharmaceutical manufacturing is usually accomplished using batch processing with laboratory testing of samples at various stages of manufacturing to evaluate quality. The FDA believes that opportunities exist for improving the development, manufacturing, and quality assurance steps through innovation in product and process development, process control, and analysis.

Typically, the pharmaceutical industry has been reluctant to try something new due to the fear that the new approach will not find favor with the FDA. An FDA rejection would result in costly delays and processing revisions that industry is unwilling to risk. The FDA now says that this hesitancy is undesirable from a public health perspective and it would like to see more innovation introduced. According to the FDA, pharmaceutical manufacturing should be based on:

- The design of effective and efficient manufacturing processes
- Product and process specifications based on an understanding of how formulation and process factors affect product performance
- Continuous real-time quality assurance
- Relevant regulatory policies and procedures tailored to accommodate the most current level of scientific knowledge
- Risk-based regulatory approaches that recognize:
  - The level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance
  - The capability of process control strategies to prevent or mitigate the risk of producing a poor-quality product

It is the intent of this guidance to facilitate progress to this state. So far, the FDA’s stated goal is not being met. FDA representatives have stated the agency’s concern about the failure of industry to rush to implement change. However, the economies of change continue to favor the status quo.

1.1.4.1 PAT Framework

Quality should be built into pharmaceutical products through a comprehensive understanding of:

- Intended therapeutic objectives, patient population, route of administration, and pharmacokinetic characteristics of a drug
- Chemical, physical, and biopharmaceutic characteristics of a drug
- Design of a product and selection of product components and packaging based on drug attributes
- Design of manufacturing processes using principles of engineering, material science, and quality assurance to ensure acceptable and reproducible product quality and performance throughout a product’s shelf life
**Process Understanding**  A process is considered to be well understood when all critical sources of variability are identified and explained, variability is managed by the process, and product quality attributes can be accurately and reliably predicted.

**Principles and Tools**  Pharmaceutical manufacturing often consists of a series of unit operations, each of which is intended to change certain properties of the materials being processed. To assure these changes are acceptable and reproducible, consideration should be given to the quality attributes of incoming materials and their acceptability for the given unit operation. Most current pharmaceutical processes are based on time-defined endpoints such as “blend for ten minutes.” In some cases, these time-defined endpoints do not consider the effects of physical differences in raw materials. Processing difficulties can arise that result in the failure of a product to meet specifications even if the raw materials conform to established specifications. Use of PAT tools and principles can provide relevant information relating to physical, chemical, and biological attributes. The process understanding gained from this information will enable process control and optimization, address the limitation of the time-defined endpoints, and improve efficiency.

**PAT Tools**  There are many tools available that enable process understanding. These tools, when used within a system, can provide effective and efficient means for acquiring information to facilitate process understanding, continuous improvement, and development of risk mitigation strategies. Such tools are categorized as follows:

- Multivariate tools for design, data acquisition, and analysis
- Process analyzers
- Process control tools
- Continuous improvement and knowledge management tools

**Strategy for Implementation**  To enable successful implementation of PAT, flexibility, coordination, and communication with manufacturers are critical. The FDA believes that current regulations are sufficiently broad to accommodate these strategies. In the course of implementing the PAT framework, manufacturers may want to evaluate the suitability of a tool on experimental and/or production equipment and processes. It is recommended that risk analysis of the impact on product quality be conducted before installation. This can be accomplished within the facility’s quality system without prior notification to the agency. Data collected using an experimental tool should be considered research data. If conducted in a production facility, it should be done under the facility’s quality system. The FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental PAT tool. Its routine inspection of a firm’s manufacturing process that incorporates a PAT tool for research purposes will be based on current regulatory standards.

The FDA has posted much of the information that firms will need in order to implement a PAT program on the Web at http://www.fda.gov/cder/ops/pat.htm.

All marketing applications, amendments, or supplements to an application should be submitted to the appropriate Center for Drug Evaluation and Research (CDER) or Center for Veterinary Medicine (CVM) division in the usual manner. In general,
PAT implementation plans should be risk based. The FDA has suggested the following possible implementation plans, where appropriate:

- PAT can be implemented under the facility’s own quality system. CGMP inspections by the PAT team or PAT-certified investigator can precede or follow PAT implementation.
- A supplement [Changes Being Expected (CBE), Changes Being Expected in 30 Days (CBE-30), or Prior Approval Supplement (PAS)] can be submitted to the agency prior to implementation, and, if necessary, an inspection can be performed by a PAT team or PAT certified investigator before implementation.
- A comparability protocol can be submitted to the agency outlining PAT research, validation and implementation strategies, and time lines. Following approval of this comparability protocol by the agency, one or a combination of the above regulatory pathways can be adopted for implementation.

To facilitate adoption or approval of a PAT process, manufacturers may request a preoperational review of a PAT manufacturing facility and process by the PAT team by contacting the FDA Process Analytical Technology Team at PAT@cdr.fda.gov. It should be noted that when certain PAT implementation plans neither affect the current process nor require a change in specifications, several options can be considered. Manufacturers should evaluate and discuss with the agency the most appropriate option for their situation.

1.1.5 GUIDANCE FOR INDUSTRY: PART 11. ELECTRONIC RECORDS; ELECTRONIC SIGNATURES—SCOPE AND APPLICATION

Of the many regulations written by the FDA, the least understood is undoubtedly 21 CFR Part 11. Rather than review the regulation itself, which is under review and possible revision, we will review the guidance for industry that FDA published in August 2003 to “aid” industry in their puzzlement. Depending on the source, it appears to be questionable as to whether this guidance document aids or confuses. It exists, however, and like it or not, understand it or not, the regulation must be followed.

The guidance indicates that the FDA’s approach is based on three main components:

- The regulation will be interpreted narrowly. Fewer records will be considered subject to Part 11.
- Those records that are considered subject to Part 11 will be subject to enforcement discretion with regard to the requirements for validation, audit trails, record retention, and record copying in the manner described and with regard to all Part 11 requirements for systems that were operational before the effective date of this regulation.
- All predicate rule requirements will be enforced. This includes record and record-keeping requirements.

The FDA does intend to enforce all other provisions of Part 11, including certain controls for closed systems. The following controls and requirements will be enforced:
Limiting system access to authorized individuals
Use of operational system checks
Use of authority checks
Use of device checks
Determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
Establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
Appropriate controls over systems documentation
Controls for open systems corresponding to controls for closed systems
Requirements related to electronic signatures

Part 11 Records  Under the narrow interpretation, the FDA considers Part 11 to be applicable to the following records or signatures in electronic format:

1. Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format in place of paper format.
2. Records that are required to be maintain under predicate rules, that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities.
3. Records submitted to the FDA under predicate rules in electronic format. However, a record that is not itself submitted but is used in generating a submission is not a Part 11 record.
4. Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required.

FDA’s Approach to Specific Part 11 Requirements

1. Validation  With respect to validation, the agency intends to exercise enforcement discretion regarding specific Part 11 requirements. However, compliance with all applicable predicate rules for validation is still expected. The FDA suggests an approach to validation be based on a justified and documented risk assessment and a determination of the potential of the system to affect product quality, safety, and record integrity.
2. Audit Trail  The agency also intends to exercise enforcement discretion regarding specific requirements related to computer-generated, time-stamped audit trails and any corresponding requirements in Part 11. Compliance with all applicable predicate rule requirements related to documentation of date, time, or sequencing of events is still expected. It is also required to comply with rules for ensuring that changes to records do not obscure previous entries.
3. Legacy Systems  The FDA intends to exercise enforcement discretion with respect to all Part 11 requirements for systems that otherwise were operational prior to August 20, 1997. Thus they do not intend to take enforcement action to enforce compliance with any Part 11 requirements if all of the following criteria are met for a specific system:
• The system was operational before the effective date.
• The system met all applicable predicate rule requirements before the effective date.
• The system currently meets all applicable predicate rule requirements.
• There is documented evidence and justification that the system is fit for its intended use.

4. Copies of Records  Enforcement discretion will be applied with respect to specific Part 11 requirements for generating copies of records and any corresponding requirements in this part. An investigator should be provided with reasonable and useful access to records during an inspection. All records held by a manufacturer are subject to inspection.

5. Record Retention  The FDA intends to exercise enforcement discretion with regard to the Part 11 requirements for the protection of records to enable their accurate and ready retrieval at any time throughout the records retention period.

1.1.6 GUIDANCE FOR INDUSTRY AND FDA: CURRENT GOOD MANUFACTURING PRACTICE FOR COMBINATION PRODUCTS

This document discusses the applicability of GMPs to combination products as defined under 21 CFR 3.2(e). Manufacturers must ensure that the product is not adulterated; the product possesses adequate strength, quality, identity, and purity; and the product complies with performance standards as appropriate. This guidance does not address technical manufacturing methods or make recommendations for manufacturers’ selection of facilities used in manufacturing.

A combination product is a product composed of a drug and a device, a biological product and a device, a drug and a biological product, or a drug, a device, and a biological product. For the purposes of this document, a constituent part of a combination product is an article in a combination product that can be distinguished by its regulatory identity as a drug, device, or biological product.

For regulatory purposes, a combination product is assigned to an agency center or alternative organizational component that will have primary jurisdiction for its premarket review and regulation. Manufacturers will be required to use the applicable GMP for their products. Regulations that may apply are:

• GMP regulations for finished pharmaceuticals (21 CFR Parts 210 and 211).
• Quality system regulations for devices (21 CFR Part 820).
• The biological product regulations (21 CFR Parts 600–680) may also apply to the manufacture of drugs that are also biological products along with the drug provisions.

There are no GMP regulations specifically for combination products. Until such regulations are promulgated, the manufacture of each constituent part is governed by the regulations for that component.

The Office of Combination Products is available as a resource to sponsors throughout the lifecycle of a combination product. This office can be reached at
1.1.7 GUIDANCE FOR INDUSTRY: POWDER BLENDS AND FINISHED DOSAGE UNITS—STRATIFIED IN-PROCESS DOSAGE UNIT SAMPLING AND ASSESSMENT

This guidance is intended to assist manufacturers in meeting the GMP requirements for demonstrating the adequacy of mixing to ensure uniformity of in-process powder blends and finished dosage units.

Stratified Sampling In this process dosage units are sampled at predefined intervals and representative samples collected from specifically targeted locations in the compression/filling operations that have the greatest potential to yield extremes of drug concentration.

This guidance describes methods of sampling that might be used to demonstrate active ingredient homogeneity. These methods are put forward as suggestions and are not intended to be the only methods for meeting FDA requirements for demonstration of the adequacy of a powder mix.

Assessment of Powder Mix Uniformity The following procedures are recommended:

1. Conduct blend analysis on batches by extensively sampling the mix in the blender and/or intermediate bulk containers.
2. Identify appropriate blending time and speed ranges, dead spots in blenders, and locations of segregation in intermediate bulk containers (IBCs).
3. Define the effects of sample size (1–10 times the dosage unit range) while developing a technique capable of measuring the true uniformity of the blend. Sample quantities larger than 3 times the dosage size can be used with adequate scientific justification.
4. Design blend-sampling plans and evaluate them using appropriate statistical analyses.
5. Quantitatively measure any variability that is present among the samples. Attribute the sample variability to either lack of uniformity of the blend or sampling error. Significant variances in the blend data within a given location can be an indication of one factor or a combination of factors such as inadequacy of blend mix, sampling error, or agglomeration. Significant between-location variance can indicate that the blending operation is inadequate.

Correlation of Powder Mix Uniformity with Stratified In-Process Dosage Unit Data The following steps are recommended for correlation:

1. Conduct periodic sampling and testing of the in-process dosage units by sampling them at defined intervals and locations throughout the compression or filling process. Use a minimum of 20 appropriately spaced in-process dosage
unit sampling points. There should be at least 7 samples taken from each of these locations for a total minimum of at least 140 samples.

2. Take 7 samples from each additional location to further assess each significant event, such as filling or emptying of hoppers and IBCs, start and end of the compression or filling process, and equipment shutdown. This may be accomplished by using process development batches, validation batches, or routine manufacturing batches for approved products.

3. Significant events may also include observations or changes from one batch to another (e.g., batch scale-up and observations of undesirable trends in previous batch data).

4. Prepare a summary of the data and analysis used to correlate the stratified sampling locations with significant events in the blending process.

5. Compare the powder mix uniformity with the in-process dosage unit data described above.

6. Investigate any discrepancies observed between powder mix and dosage unit data and establish root causes. At least one troubleshooting guide is available that may be helpful with this task. Possible corrections may range from going back to formulation development to improve powder characteristics to process optimization. Sampling problems may also be negated by use of alternate state-of-the-art methods of in situ real-time sampling and analysis.

Correlation of Stratified In-Process Samples with Finished Product

The following steps are recommended:

1. Conduct testing for uniform content of the finished product using an appropriate procedure or as specified in the ANDA or the NDA for approved products.

2. Compare the results of stratified in-process dosage unit analysis with uniform content of the finished dosage units from the previous step. This analysis should be done without weight correction.

3. Prepare a summary of the data and analysis used to conclude that the stratified in-process sampling provides assurance of uniform content of the finished product.

1.1.7.1 Validation of Batch Powder Mix Homogeneity

This section describes sampling and testing the powder mix of demonstration and process validation batches used to support implementing the stratified sampling method described in this guidance.

The guidance document recommends that during the manufacture of demonstration and process validation batches, the following uniformity characteristics be assessed: (1) the powder blend, (2) the in-process dosage units, and (3) the finished product. Each attribute should be determined independently. It is further recommended that the following steps be used to identify sampling locations and acceptance criteria prior to the manufacture of the exhibit and/or validation batches:
1. Carefully identify at least 10 sampling locations in the blender to represent potential areas of poor blending. For example, in tumbling blenders (such as V-blenders, double cones, or drum mixers), samples should be selected from at least two depths along the axis of the blender. For convective blenders (such as a ribbon blender), a special effort should be made to implement uniform volumetric sampling to include the corners and discharge area (at least 20 locations are recommended to adequately validate convective blenders).

2. Collect at least three replicate samples from each location. Samples should meet the following criteria:
   - Assay one sample per location (number of samples \( n = 10 \), or \( n = 20 \) for ribbon blender).
   - RSD (relative standard deviation) of all individual results is 5.0%.
   - All individual results are within 10.0% (absolute) of the mean of the results.

It is also recommended that you not proceed any further with implementation of the methods described in this guidance until the criteria are met.

Sampling errors may occur in some powder blends, sampling devices, and techniques that make it impractical to evaluate adequacy of mix using only the blend data. In such cases, it is recommended that in-process dosage unit data be used in conjunction with blend sample data to evaluate blend uniformity.

Some powder blends may present an unacceptable safety risk when directly sampled. The safety risk, once described, may justify an alternate procedure. In such cases, process knowledge and data from indirect sampling combined with additional in-process dosage unit data may be adequate to demonstrate the adequacy of the powder mix. Data analysis used to justify using these alternate procedures should be described in a summary report that is maintained at the manufacturing facility.

1.1.7.2 Verification of Manufacturing Criteria

The assessment of powder mix uniformity and correlation of stratified in-process dosage unit sampling development procedures should be completed before establishing the criteria and controls for routine manufacturing. It is also recommend that the normality be assessed and that the RSD be determined from the results of stratified in-process dosage unit sampling and testing that were developed. The RSD value should be used to classify the testing results as either readily pass (RSD 4.0%), marginally pass (RSD 6.0%), or inappropriate for demonstration of batch homogeneity when RSD > 6.0%.

The FDA recommends that routine manufacturing batches be evaluated against the following criteria after completing the procedures described above to assess the adequacy of the powder mix and uniform content in the finished dosage form:

1. Standard criteria method (SCM)—This method is recommended when either of the following conditions is met:
   1.1. Results of establishing initial criteria are classified as readily pass.
1.2. Results of testing to the marginal criteria method (MCM) pass the criteria for switching to the SCM.

1.2.1. **Stage 1 Test** To perform the stage 1 test, collect at least three dosage units from each sampling location, assay one dosage unit from each location, weight correct the results, and compare the results with the following criteria:

- 1.2.1.1. RSD of all individual results is less than 5%.
- 1.2.1.2. Mean of all results is 90–110% of target assay.

If the results pass these criteria and the adequacy of mix and uniformity of dosage unit content for the batch are adequate, the SCM can be used for the next batch. If test results fail stage 1 criteria, extended testing to stage 2 is required.

1.2.2. **Stage 2 Test** To perform the stage 2 test, assay the remaining two dosage units from stage 1 for each sampling location and compute the mean and RSD of data combined from both stage 1 and stage 2. Compare the results with the following criteria:

- 1.2.2.1. For all individual results, the RSD should be less than 5.0%.
- 1.2.2.2. Mean of all results is 90–110% of target assay.

If results pass the above criteria, the adequacy of mix and uniformity of content for the batch are adequate and stage 1 can be used for the next batch. If test results fail the criteria, use the MCM described in the section below.

2. Marginal criteria method—The MCM can be used when either of the following conditions is met:

- 2.1. Results of initial criteria establishment qualified as *marginally pass*.
- 2.2. Results of initial criteria establishment qualified as *readily pass* or a batch was tested according to SCM and the test results failed both stage 1 and stage 2 criteria.
- 2.3. If either of the above two criteria apply, use the weight corrected results from the stage 2 SCM analysis and compare this with the MCM criteria:
  - 2.3.1. For all individual results, the RSD is less than 6.0%.
  - 2.3.2. The mean of all results is 90.0–110.0% of target assay.
- 2.4. It is acceptable to switch to the SCM when five consecutive batches pass the MCM criteria and result in RSD of less than 5.0%.

### 1.1.8 GUIDANCE FOR INDUSTRY: IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS SCALE-UP AND POSTAPPROVAL CHANGES (SUPAC)—CHEMISTRY, MANUFACTURING AND CONTROLS, IN VITRO DISSOLUTION TESTING, AND IN VIVO BIOEQUIVALENCE DOCUMENTATION

This guidance provides recommendations to NDA and ANDA sponsors who intend to make changes to the product during the postapproval period. Changes include any change in components or composition of the product, the site of manufacture, the scale-up/scale-down of batch size, and/or the manufacturing process and/or equipment of an immediate-release oral formulation.
Changes in Components (Excipients) and Composition

Changes in the amount or source of drug substance are not addressed by this guidance. Changes in components or composition that have the effect of adding a new excipient or deleting an excipient are defined at level 3 except as described below:

1. Level 1 changes
   1.1. Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.
   1.2. Allowed changes (changes that can be made without prior FDA approval) are shown below. This is based on the assumption that the drug substance in the product is formulated to 100% of label potency. To be considered a level 1 change, the total additive effect of all excipient changes should not be more than 5% relative to the target dosage form weight.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Percentage of Excipient (W/W) Out of Total Target Dosage Form Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filler</td>
<td>±5</td>
</tr>
<tr>
<td>Disintegrant</td>
<td></td>
</tr>
<tr>
<td>Starch</td>
<td>±3</td>
</tr>
<tr>
<td>Other</td>
<td>±1</td>
</tr>
<tr>
<td>Binder</td>
<td></td>
</tr>
<tr>
<td>Calcium or magnesium Stearate</td>
<td>±0.25</td>
</tr>
<tr>
<td>Other</td>
<td>±1</td>
</tr>
<tr>
<td>Glidant</td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>±1</td>
</tr>
<tr>
<td>Other</td>
<td>±0.1</td>
</tr>
<tr>
<td>Film coat</td>
<td>±1</td>
</tr>
</tbody>
</table>

1.3. Test documentation
   1.3.1. Chemistry—Application/compendial release requirements and stability testing. For stability testing, one batch should be on long-term stability testing with data being reported in the annual report.
   1.3.2. Filing documentation—All information must be included in the annual report (including long-term stability data).

2. Level 2 changes
   2.1. Level 2 changes are those that could have a significant impact on formulation quality and performance. Tests and filing documentation for a level 2 change depend on three factors: (1) therapeutic range, (2) solubility, and (3) permeability. Therapeutic range is defined as either narrow or nonnarrow. Drug solubility and drug permeability are defined as either low or high. Changes in excipients, expressed as percent (w/w) of total formulation, greater than those listed for a level 1 change but less than or equal to the following percent ranges are acceptable level 2 changes:
<table>
<thead>
<tr>
<th>Excipient</th>
<th>Percentage of Excipient (w/w) of Total Target Dosage Form Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filler</td>
<td>±10</td>
</tr>
<tr>
<td>Disintegrant</td>
<td></td>
</tr>
<tr>
<td>Starch</td>
<td>±6</td>
</tr>
<tr>
<td>Other</td>
<td>±2</td>
</tr>
<tr>
<td>Binder</td>
<td>±1</td>
</tr>
<tr>
<td>Lubricant</td>
<td></td>
</tr>
<tr>
<td>Ca or Mg stearate</td>
<td>±0.5</td>
</tr>
<tr>
<td>Other</td>
<td>±2</td>
</tr>
<tr>
<td>Glidant</td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>±2</td>
</tr>
<tr>
<td>Other</td>
<td>±0.2</td>
</tr>
<tr>
<td>Film coat</td>
<td>±2</td>
</tr>
</tbody>
</table>

These percentages are based on the assumption that the drug substance in the finished product is formulated to 100% of labeled potency. The total additive effect of all excipient changes should not change by more than 10%.

All components in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are based. Allowable changes in the composition should be based on the approved target composition and not on the composition based on previous level 1 or level 2 changes.

2.2. Test documentation

2.2.1. Chemistry

2.2.1.1. Application/compendial release requirements and batch records.

2.2.1.2. Stability testing—Test one batch with three months of accelerated stability data in supplement and on batch on long-term stability.

2.2.2. Dissolution

2.2.2.1. High-permeability, high-solubility drugs—Dissolution of 85% in 15 min in 900 mL of 0/1 HCl. If a drug product fails to meet this criterion, tests in 2.2.2.2 or 2.2.2.3 below should be performed.

2.2.2.2. Low-permeability, high-solubility drugs—Multipoint dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60, and 120 min or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.

2.2.2.3. High-permeability, low-solubility drugs—Multipoint dissolution profiles should be performed in water, 0.1 HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five different profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 min until either 90% of drug from the drug product is
dissolved or an asymptote is reached. A surfactant may be used, but only with appropriate justification. The dissolution profile of the proposed and currently used product formulations should be similar.

2.2.3. In vivo bioequivalence documentation is not required for level 2. If the product does not meet any of the level 1 cases above, refer to level 3 changes.

2.2.4. Filing documentation—A prior approval supplement with all data including the accelerated stability data is required. This change should also be documented in the annual report along with the long-term stability data.

2.3. Level 3 changes

2.3.1. Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. Tests and filing documentation vary depending on the following three factors: therapeutic range, solubility, and permeability. For example:

2.3.1.1. Any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges specified in the level 1 table.

2.3.1.2. All other drugs not meeting the dissolution criteria under level 2.

2.3.1.3. Changes in the excipient ranges of low-solubility, low-permeability drugs beyond those listed in level 1.

2.3.1.4. Changes in the excipient ranges of all drugs beyond those listed in the level 2 table.

2.3.2. Test documentation

2.3.2.1. Chemical

(a) Application/compendial release requirements and batch records:

- Information available—One batch with three months accelerated stability data reported in a supplement and one batch on long-term stability reported in the annual report.
- Information NOT available—Up to three batches with three months accelerated stability data reported in the supplement and one batch on long-term stability data reported in annual report.

(b) Dissolution documentation—Case B dissolution profile as described in the table for level 2.

(c) In vivo bioequivalence documentation—Full bioequivalence study. This requirement may be waived with a verified acceptable in vivo/in vitro correlation.

2.3.2.2. Filing documentation—Prior approval supplement including accelerated stability data plus an annual report showing long-term stability data.

Site Changes Site changes are changes in the location of manufacture for both company-owned and contract manufacturing facilities. A site change does not
include, for example, scale-up changes, changes in manufacturing equipment or a manufacturing process, and changes in Standard Operating Procedures (SOPs) or environmental changes. Each change must be considered separately.

1. Level 1 changes—A level 1 change consists of a site change within a single facility where the same equipment, SOPs, environmental conditions, and personnel are used and where no changes are made to the manufacturing batch records other than location of the facility and administrative changes.
   1.1. Required documentation—No documentation is required beyond the usual application/compendial requirements. No in vivo bioequivalence documentation is required.
   1.2. Filing requirements—Annual report.
2. Level 2 changes—A level 2 change is a site change within a contiguous campus or between facilities in adjacent city blocks where the same equipment, SOPs, environmental conditions and controls, and personnel common to both manufacturing sites are used. There must be no changes to the manufacturing batch records except for administrative information and the location of the facility.
   2.1. Required documentation
      2.1.1. Chemistry—Identify location of new site and updated batch records. No other documentation is required beyond application/compendial release requirements, although one batch produced at the new site should be placed on long-term stability and the data should be reported in the annual report. Dissolution data other than normal release requirements are not required nor is in vivo bioequivalence testing required.
      2.1.2. Filing documentation—A supplement should be filed showing the changes being effected. Long-term stability test data should be included in the annual report.
3. Level 3 changes—A level 3 change is a change in manufacturing site to a different campus. However, the same equipment, SOPs, environmental conditions, and controls should be used in the manufacturing process at the new site. No changes may be made to the manufacturing batch records except for administrative information, location, and language translation if needed.
   3.1. Documentation
      3.1.1. Chemistry—Location of new site and updated batch records.
      3.1.2. Stability
         3.1.2.1. If a significant body of data is available, one batch with three months accelerated stability data must be reported in a supplement. One batch should be on long-term stability with the stability data reported in the annual report.
         3.1.2.2. If a significant body of data is not available, up to three batches with three months accelerated stability data should be reported in the supplement. Up to three batches should be on long-term stability with these data being reported in the annual report.
      3.1.3. Dissolution—A multipoint dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60, and 120 min or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.
      3.1.4. In vivo bioequivalence—None required.
3.2. Filing documentation required—Changes being effected should be identified in a supplement. Long-term stability data are reported in the annual report.

Changes in Batch Size  Postapproval changes in the size of a batch from the pilot scale used to manufacture product for clinical trials to larger or smaller commercial batch sizes require submission of additional information in the application. Scale-down below 100,000 dosage units is not covered by this guidance. All scale-up changes should be properly validated and, where needed, inspected by appropriate FDA personnel.

1. Level 1 changes—A change in batch size, up to and including a factor of 10 times the size of the pilot batch, is considered a level 1 change. However, (1) the equipment used must be of the same design and operating principles, (2) the product is manufactured in full compliance with the prevailing GMPs, and (3) the same formulation and manufacturing procedures are used as well as the same SOPs and controls.
   1.1. Chemistry documentation—(1) Application/compendial release requirements, (2) notification of change to the FDA and submission of updated batch records in the annual report, and (3) one batch should be on long-term stability with results being provided in the annual report.
   1.2. Dissolution documentation—None beyond application/compendial release requirements.
   1.3. In vivo bioequivalence—None.
   1.4. Filing documentation—Annual report with long-term stability data.

2. Level 2 changes—Level 2 consists of changes in batch size beyond a factor of 10 times the size of the pilot batch where (1) the equipment used to produce the pilot batches is of the same design and operating principles, (2) the product is manufactured in full compliance with the prevailing GMPs, and (3) the same formulation and manufacturing procedures are used as well as the same SOPs and controls.
   2.1. Chemistry—Application/compendial release requirements. Notification of change in batch size and submission of updated batch records to the FDA. One batch must be placed on accelerated stability testing and one on long-term stability.
   2.2. Dissolution—None beyond application/compendial release requirements.
   2.3. In vivo bioequivalence—None.
   2.4. Filing requirements—Must submit changes being effected in the supplement. Long-term stability data are reported in the annual report.

Manufacturing  Manufacturing changes may be either the equipment used in the manufacturing process or the process itself:

1. Equipment
   1.1. Level 1 equipment changes—This category includes change from the use of nonautomated or nonmechanical equipment to automated or mechanical equipment to move ingredients and a change to alternative equipment of the same design and operating principles of the same or different capacity.
1.1. Chemistry documentation—Application/compendial release requirements, notification of change, and submission of updated batch records. One batch should be placed on long-term stability.

1.1.2. Dissolution documentation—None other than application/compendial release requirements.

1.1.3. In vivo bioequivalence documentation—None.

1.1.4. Filing documentation—Annual report with long-term stability data.

1.2. Level 2 equipment changes—This type of change involves a change in equipment to a different design and different operating principles.

1.2.1. Chemistry documentation—Application/compendial release requirements, notification of change, and submission of updated batch records.

1.2.1.1. If a significant body of data are available, one batch with three months of accelerated stability data reported in the supplement and one batch on long-term stability with data reported in the annual report.

1.2.1.2. If a significant body of data are not available, submit up to three batches with three months accelerated stability data in the supplement and up to three batches on long-term stability with data reported in the annual report.

1.2.2. Dissolution documentation—A multipoint dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60, and 120 min or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.

1.2.3. In vivo bioequivalence documentation—None.

1.2.4. Filing documentation—Prior approval supplement with justification for change; long-term stability data must be reported in the annual report.

2. Process changes

2.1. Level 1 process changes—This includes process changes such as changes in mixing times and operating speeds within application/validation ranges.

2.1.1. Chemistry documentation—None beyond application/compendial release requirements.

2.1.2. Dissolution documentation—None beyond application/compendial release requirements.

2.1.3. In vivo bioequivalence documentation—None.

2.1.4. Filing documentation—Annual report.

2.2. Level 2 process changes—Level 2 changes include process changes such as mixing times and operating speeds outside of application/validation ranges.

2.2.1. Chemistry documentation—Application/compendial release requirements; notification of change and submission of updated batch records. One batch on long-term stability.

2.2.2. Dissolution documentation—A multipoint dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60, and 120 min or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.
2.2.3. In vivo bioequivalence documentation—None.
2.2.4. Filing documentation—A supplement with changes being effected. Long-term stability data should be reported in the annual report.

2.3. Level 3 process changes—Level 3 includes change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression.

2.3.1. Chemistry documentation—Application/compendial release requirements. Notification of change and submission of updated batch records. Stability testing varies depending on the amount of data available:
2.3.1.1. Significant body of data available—One batch with three months accelerated stability data should be reported in the supplement; one batch should also be put on long-term stability with data being reported in the annual report.
2.3.1.2. No significant body of data available—Up to three batches with three months accelerated stability data should be reported in the supplement. Up to three batches should be on long-term stability with data being reported in the annual report.

2.3.2. Dissolution documentation—A multipoint dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60, and 120 min or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.

2.3.3. In vivo bioequivalence documentation—An in vivo bioequivalence study should be performed. This may be waived if a suitable in vivo/in vitro correlation has been verified.

2.3.4. Filing documentation—A prior approval supplement must be filed with justification for the change. Long-term stability data should be submitted in the annual report.

1.1.9 OTHER GMP-RELATED GUIDANCE DOCUMENTS

This chapter has discussed the CGMP regulations and some of the more important guidances. There have been a number of additional guidance documents related to GMPs published by the FDA. These documents are all posted on the FDA website. They are listed below along with their URL:

- Questions and answers on current good manufacturing practices (cGMP) for drugs: http://www.fda.gov/cder/guidance/cGMPs/default.htm
- Powder blends and finished dosage units—Stratified in-process dosage unit sampling and assessment: http://www.fda.gov/cder/guidance/5831dft.pdf
• General principles of process validation: http://www.fda.gov/cder/guidance/pv.htm
• SUPAC-MR: Modified release solid oral dosage forms scale-up and postapproval changes: Chemistry, manufacturing, and controls; in vitro dissolution testing and in vivo bioequivalence documentation: http://www.fda.gov/cder/guidance/1214fnl.pdf
• SUPAC-SS: Nonsterile semisolid dosage forms; scale-up and post-approval changes: Chemistry, manufacturing and controls; in vitro release testing and in vivo bioequivalence documentation: http://www.fda.gov/cder/guidance/1447fnl.pdf