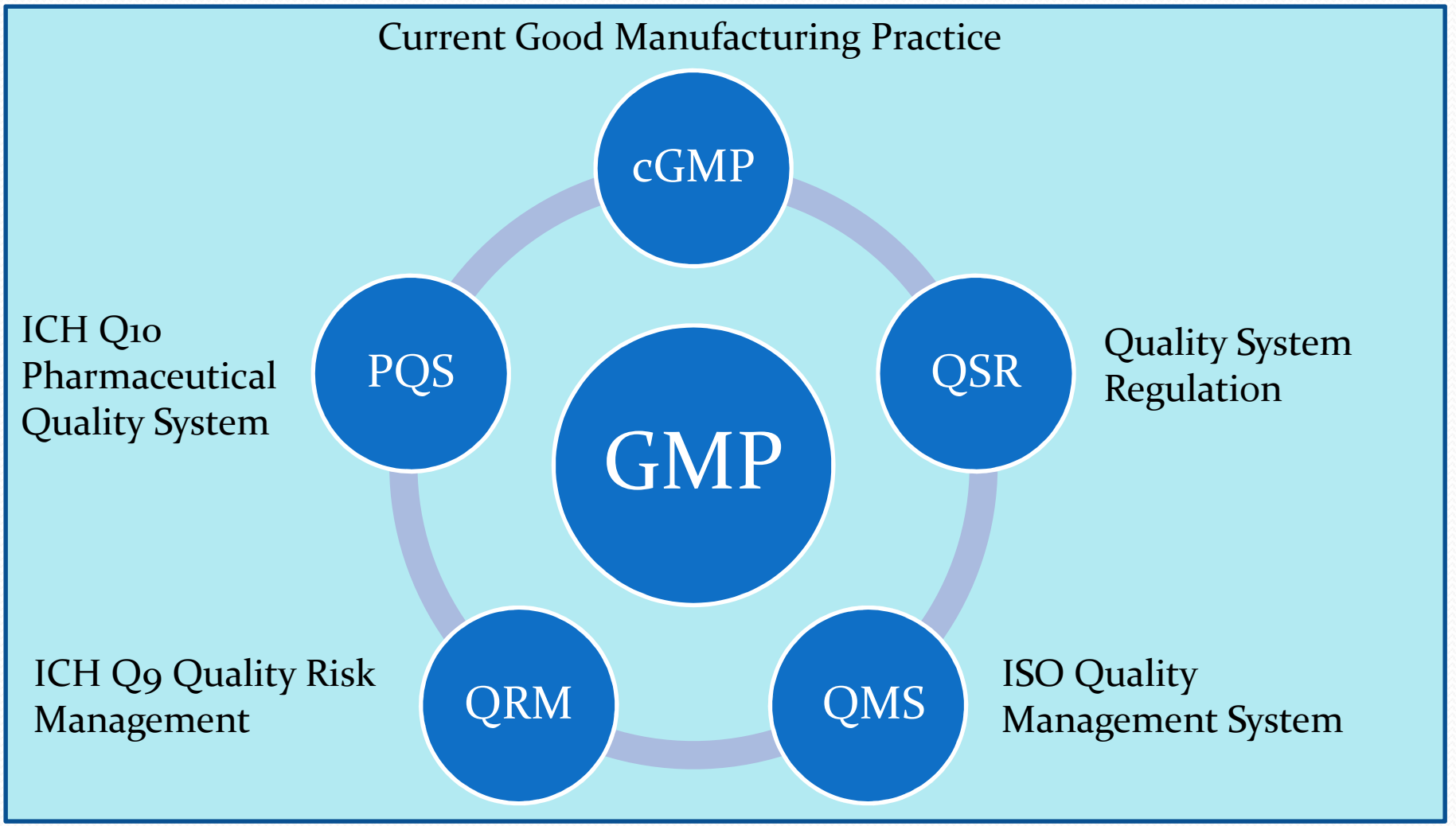
Glisland® Training Series:

Good Manufacturing Practice

Glisland, Inc.
San Jose, California, USA
http://www.glisland.com

Welcome to the Drug GMP World



FDA Drug GMP Regulations

1. 21 CFR Part 210 (General)
2. 21 CFR Part 211 (Finished pharmaceuticals)
3. 21 CFR Part 216 (Pharmacy compounding)
4. 21 CFR Part 225 (Medicated feeds)
5. 21 CFR Part 226 (Type A medicated articles)
6. 21CFR Part 600-680 (Biologics)
7. 21 CFR Part 1271 (Human cells, tissues, and cellular and tissue-based products (HCT/P's))

Website to download 21 CFR:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm

21 CFR Part 211 Components

1. Organization and Personnel
2. Buildings and Facilities
3. Equipment
4. Components and Drug Product Containers and Closures
5. Production and Process Controls
6. Packaging and Labeling Control
7. Holding and Distribution
8. Laboratory Controls
9. Records and Reports
10. Returned and Salvaged Drug Products

-Organization and Personnel

1. **Quality control unit**
   a) Responsibility and authority
   b) Adequate laboratory facilities
   c) Written responsibilities and procedures
2. **Personnel qualifications**
   a) Education, training, experience
   b) Continuing cGMP training
   c) Adequate number of qualified personnel

3. **Personnel responsibilities**
   a) Clean clothing, protective apparel
   b) Good sanitation and health habits
   c) Limited-access
   d) Health conditions
4. **Consultants**
   a) Sufficient education, training, experience
   b) Name, address, qualifications, type of service

-Buildings and Facilities

1. **Design and construction features**
   a) Suitable size, construction and location
   b) Adequate space and flow to prevent mixups and contamination
   c) Specifically defined areas for different operations to prevent contamination or mixups
   d) Separate facility for penicillin operations
2. **Lighting**

   Adequate lighting in all areas

3. **Ventilation, air filtration, air heating and cooling**
   a) Adequate ventilation
   b) Adequate control over air pressure, micro-organisms, dust, humidity, and temperature
   c) Air filtration systems and exhaust systems to control contaminants
   d) Separate air-handling systems for penicillin

4. **Plumbing**
   a) Potable water pressure and standard
   b) Drains
5. **Sewage and refuse**

   Dispose in a safe and sanitary manner
6. **Washing and toilet facilities**

   Hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas

7. **Sanitation**
   a) Maintained in a clean and sanitary condition
   b) Written procedures
8. **Maintenance**

   Maintained in a good state of repair

-Equipment

1. **Equipment design, size, and location**
   a) Appropriate design
   b) Adequate size
   c) Suitably located
2. **Equipment construction**
   a) Surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive
   b) Free of contamination from operation substances such as lubricants or coolants

3. **Equipment cleaning and maintenance**
   a) Cleaning schedule
   b) Written procedures
   c) Records
4. **Automatic, mechanical, and electronic equipment**
   a) Calibration, performance check
   b) Appropriate controls
   c) Input/output accuracy check
   d) Data backup
   e) One person performance check

5. Filters

- Prevent filter fibers from releasing into injectable drug products
- Avoid using fiber releasing filters when possible
- The use of an asbestos-containing filter is prohibited

-Components, Containers, and Closures

1. **General requirements**
   1) Written procedures
   2) Contamination prevention
   3) Bagged or boxed components
   4) Identification code (control number) and lot status
2. **Receipt and storage of untested components, drug product containers, and closures**
   a) Visual inspection
   b) Quarantine before testing or exam

3. **Testing and approval or rejection of components, drug product containers, and closures**
   a) Withhold for use until release
   b) Sampling plan
   c) Sample collection
   d) Sample examination/testing
   e) Specifications for release or reject

4. **Use of approved components, drug product containers, and closures**

   Rotation: the oldest approved stock is used first.

5. **Retesting of approved components, drug product containers, and closures**

   Retest when necessary (e.g. storage for long time)

6. **Rejected components, drug product containers, and closures**

   Quarantine rejected ones

7. Drug product containers and closures

a) Not reactive/additive/absorptive

b) Adequate protection

c) Clean, sterilized, and processed to remove pyrogenic properties

d) Specifications and written procedures

-Production and Process Controls

1. **Written procedures; deviations**
   a) Written procedures shall be drafted, reviewed and approved by appropriate organization units then reviewed and approved by QA
   b) Any deviation from written procedures shall be recorded and justified

-Production and Process Controls

2. **Charge-in of components**

   Assuring identity, strength, quality, and purity of drug products:

   a) Batch formulation should contain not less than 100% required API
   b) Weigh, measure, subdivide, and label as appropriate
   c) Exam component dispense by a second person
   d) Verify adding of component to the batch by a second person

-Production and Process Controls

3. **Calculation of yield**

   Calculation of yield of each phase shall be performed by one person and independently verified by a second person.

4. **Equipment identification**

   a) Identify at all time to indicate their contents and/or phase of processing of the batch

   b) Identify equipment ID in batch record

-Production and Process Controls

5. **Sampling and testing of in-process materials and drug products**

   In-process material means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

   a) Written procedures to assure batch uniformity and integrity
   b) Valid in-process specification variability
   c) In-process materials testing
   d) Quarantine rejected in-process materials

-Production and Process Controls

6. **Time limitations on production**

   Establish time limits; justify and document deviation.

7. **Control of microbiological contamination**

   a) Written procedures to prevent objectionable microorganisms in drug products not required to be sterile.

   b) Written procedures to prevent microbiological contamination of drug products purporting to be sterile, including validation of sterilization process.

-Production and Process Controls

8. **Reprocessing**
   a) Written procedures for reprocessing nonconforming batches
   b) Review and approval by QA before reprocessing

-Packaging and Labeling Control

1. **Materials examination and usage criteria**
   a) Control the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials.
   b) Prevent nonconforming labeling or packing materials from unsuitable use.
   c) Record status of each shipment received: receipt, examination/testing, accepted/rejected.
   d) Store different labeling materials separately with access control.
   e) Destroy obsolete and outdated labeling materials.
   f) Handle gang-printing issue.
   g) Control cut labeling.
   h) Control imprinting.

-Packaging and Labeling Control

2. Labeling issuance

a) Strict control in issuing labeling to prevent mislabeling.

b) Carefully examine for identity and conformity to labeling specification in the master of batch records.

c) Reconcile the quantities of labeling issued, used, returned, and quantity of drug product to labeled.

d) Destroy excess labeling bearing lot or control numbers.

e) Prevent mixups for returned labeling.

f) Written procedures for issuance of labeling.

-Packaging and Labeling Control

3. **Packaging and labeling operations**
   a) Prevent mixups and cross-contamination.
   b) Preclude mislabeling.
   c) Apply a lot or control number.
   d) Examine and document packaging and labeling materials for its correctness before packaging.
   e) Inspect and document packaging and labeling facilities to assure drug products, packaging and labeling materials from previous operation have been removed (line clearance).

-Packaging and Labeling Control

4. **Tamper-evident packaging requirements for over-the-counter (OTC) human drug products**
   a) Risk of being adulterated and/or misbranded
   b) Requirement for a tamper-evident package
   c) Label statement requirements
   d) Exemption request
   e) Change approval
   f) Requirements from 21 CFR 310.3(l) and the Poison Prevention Packaging Act of 1970 still hold

-Packaging and Labeling Control

5. **Drug product inspection**
   a) Examine packaged and labeled products for correct label during finishing operations.
   b) Examine finished products for correct labeling from representative sample.
   c) Document the examination results in batch records.

-Packaging and Labeling Control

6. **Expiration dating**
   a) Determine and label expiration date.
   b) Relate expiration date to storage conditions stated on the labeling.
   c) Reconstituting drug product expiration information.
   d) Appear on the immediate container and also the outer package when necessary.
   e) Homeopathic drug products are exempt.
   f) Exemption of allergenic extracts.
   g) Exemption of IND drug products.
   h) Pending consideration.

-Holding and Distribution

1. **Warehousing procedures**
   a) Quarantine drug product before release by QA.
   b) Appropriate storage condition (temperature, humidity, and light).
2. **Distribution procedures**
   a) The oldest approved stock is distributed first.
   b) Track the distribution of each lot to facilitate its recall if necessary.

-Laboratory Controls

1. **General requirements**
   a) Laboratory control procedure requirements.
   b) What to establish: specifications, standards, sampling plans, test procedures.
   c) What to control: components, drug product containers, closures, in-process materials, labeling, and drug products.
   d) What to determine: conformance to specifications, procedures, and device operation standards.

-Laboratory Controls

2. **Testing and release for distribution**
   a) Batch conformance testing
   b) Batch microorganism testing
   c) Written procedures for sampling and testing plan and methods
   d) Statistical quality control and acceptance criteria
   e) Document and validate accuracy, sensitivity, specificity, and reproducibility of test methods
   f) Handling of nonconformance and reprocessing

-Laboratory Controls

3. **Stability testing**
   a) Written testing program
   b) Number of batches for testing and accelerated studies
   c) Homeopathic drug products
   d) Allergenic extracts exemption
4. **Special testing requirements**
   a) Sterile and/or pyrogen-free drug products
   b) Ophthalmic ointment
   c) Controlled-release dosage form

-Laboratory Controls

5. **Reserve samples**
   a) Representation (each lot), quantity (twice), retention time (1 year, 3 months, 6 months, 3 years).
   b) Storage condition and checking for deterioration.
6. **Laboratory animals**

   Maintain and control to assure their suitability for testing use.
7. **Penicillin contamination**

   Test non-penicillin drug product to determine cross contamination with penicillin.

-Records and Reports

1. **General requirements**
   a) Any production, control, distribution record, for at least 1 year after the expiration date of the batch, or 3 years after distribution of the batch for OTC drug product.
   b) Records of all components, drug product containers, closures, and labeling, for at least 1 year after the expiration date, or in the case of OTC drug product 3 years after distribution of the last lot of drug product.
   c) Available for inspection.
   d) Evaluation for change.
   e) Management notification.

-Records and Reports

2. **Equipment cleaning and use log**

   Show the date, time, product, and lot number of each batch processed, date and sign or initial.

3. **Component, drug product container, closure, and labeling records**

   a) Identity and quantity of each shipment of each lot, the name of supplier, the supplier's lot number(s) if known, the receiving code and date of receipt, the name of prime manufacturer.
   b) The test results.
   c) Individual inventory record.
   d) Examination and review of labels and labeling.
   e) Disposition of rejected ones.

-Records and Reports

4. **Master production and control records**
   a) Prepared, dated, and signed by one person and independently check, dated, and signed by a second person for each product to assure batch-to-bath uniformity.
   b) Include the information specified in this section.
5. **Batch production and control records**
   a) Prepared for each batch produced for accurate reproduction of the appropriate master product or control record, checked for accuracy, dated and signed.
   b) Documentation of each significant step of the batch with information specified in this section.

-Records and Reports

6. **Production record review**

   QA review and investigation of any unexplained discrepancy.

7. **Laboratory records**

   a) Include complete data as specified in this section.
   b) Any method modification.
   c) Testing and standardization of reference standards, reagents, and standard solutions.
   d) Calibration records.
   e) Stability testing records.

-Records and Reports

8. **Distribution records**

   Name and strength of the product, description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product.

9. **Complaint files**

   a) Written procedures for handling of all written and oral complaints regarding a drug product and QA review.

   b) Complaint file location, inspection, retention time, and content specified in this section.

-Returned and Salvaged Drug Products

1. **Returned drug products**

   Identified as returned, held, destroyed, reprocessed, record maintained.

2. **Drug product salvaging**

   Evidence to justify salvaging and record keeping requirements.

GMP for APIs

- API: Active Pharmaceutical Ingredient
- ICH Q7A "*ICH Harmonised Tripartite Guideline Good Manufacturing Practice guide for Active Pharmaceutical Ingredients Q7* ". ICH, November 2000 http://www.ich.org/LOB/media/MEDIA433.pdf.
- FDA "*Guidance for Industry Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*." Rockville, MD, August 2001. http://www.fda.gov/cder/guidance/4286fnl.pdf.

FDA and ICH

- ICH includes regulatory authorities from three regions: Europe, Japan and the United States
- Once an ICH guidance is adopted by FDA, it is published in the *Federal Register (e.g. E6: http://www.fda.gov/cder/guidance/959fnl.pdf)*
- FDA has website that includes ICH guidances: http://www.fda.gov/cber/ich/ichguid.htm

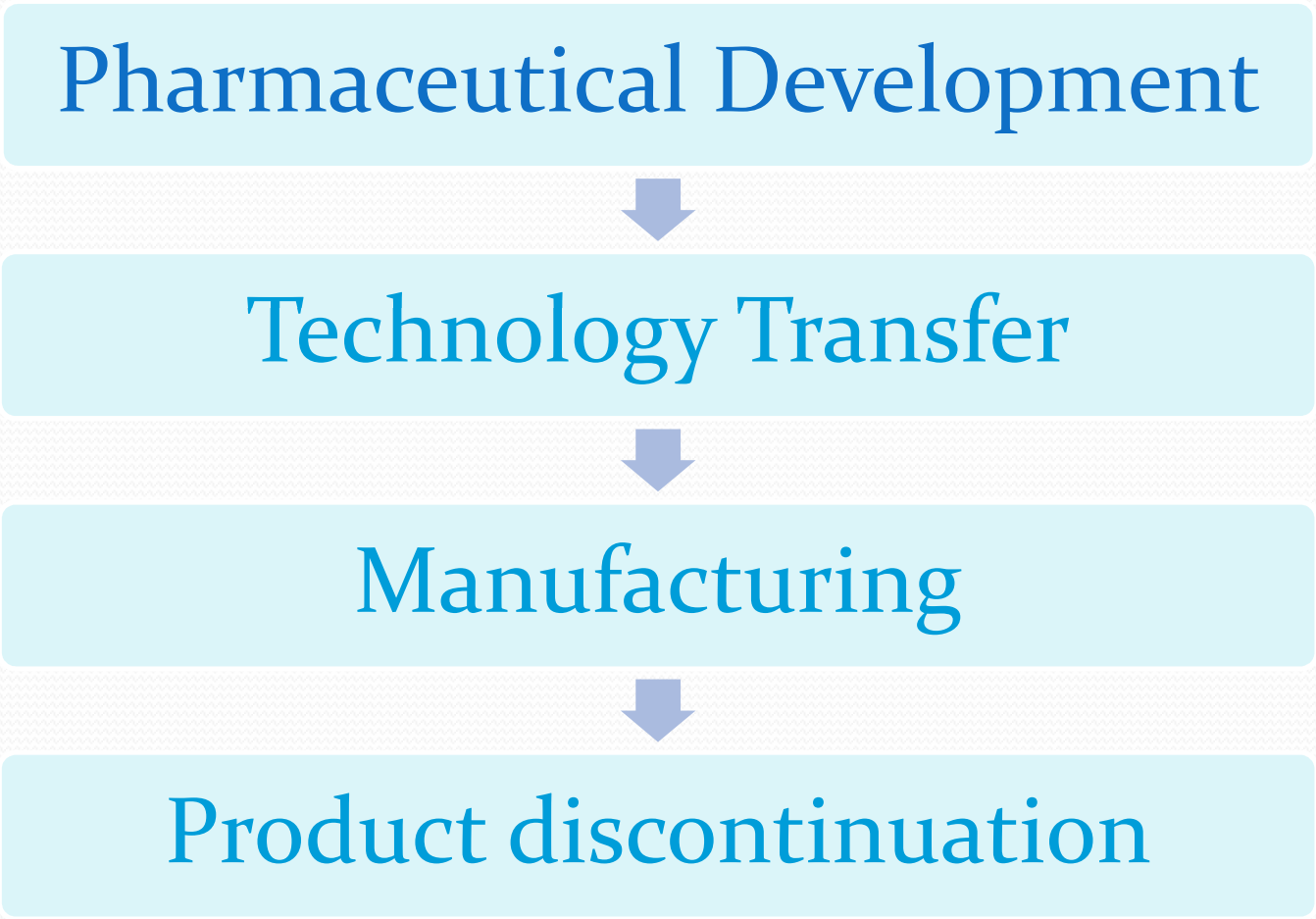
ICH Quality System Model

1. Management Responsibility.
2. A set of processes that provides a product with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities and internal customers.
3. Effective monitoring and control systems for process performance and product quality.
4. Product quality improvements, process improvements, variability reduction, innovations, and pharmaceutical quality system enhancements.
5. Applicable to pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product lifecycle.

Management Responsibility

1. Management Commitment
2. Quality policy
3. Quality Planning
4. Resource Management
5. Internal Communication
6. Management Review
7. Oversight of Outsourced Activities

Product Lifecycle



The Most Fundamental GMP Concept

"Quality cannot be 'tested into' a product; it must be designed and built in." – *Fundamentals of US Regulatory Affairs, RAPS, 2005.*

Quality system approach is an effective way to help ensure GMP compliance.

Enhancement Elements

- Process performance and product quality monitoring system;
- Corrective action and preventive action (CAPA) system;
- Change management system;
- Management review of process performance and product quality.

Risk-Based Approach

- On 10/16/02, FDA published "A Risk-Based Approach to cGMPs"
- FDA has been undertaking an initiative to use a science-based risk management and integrated quality systems approach to pharmaceutical cGMPs.
- GMP regulations based on the principle of risk-based decisions would include requirements for product based health hazard analysis of critical control points in the manufacturing process.

Quality System Approach

- FDA published guidance: “Quality Systems Approach to Pharmaceutical CGMP Regulations” in September 2006 as part of pharmaceutical cGMP.
- The guidance harmonized with ICH quality system model including risk analysis and the enhancement elements.

Amendment of cGMP

- FDA periodically reassesses and revises the CGMP regulations to accommodate advances in technology and other scientific knowledge that further safeguard the drug manufacturing process and the public health.
- FDA published the latest amendments (final rule) to 21 CFR Part 210 and 21 CFR Part 211 to modernize or clarify some of the CGMP requirements, as well as harmonize some of the CGMP requirements with those of other foreign regulators and other FDA regulations. (FR Vol. 73 No. 174, September 8, 2008).
- This new rule is effective December 8, 2008.

Changes in the Final Rule

A. Aseptic Processing

211.113(b), 211.67(a), 211.84(d)(6), 211.94(c), 211.110(a)

B. Asbestos Filters

210.3(b)(6)， 211.72，

C. Verification by a Second Individual

Certain operations may be performed by automated equipment and verified by a person, rather than one person performing an operation and another person verifying that the operation was correctly performed.

D. Other Minor Changes

FDA Enforcement Actions

- Establishment registration and product listing
- Marketing clearance/approval
- Reports
- Inspections
- Notice of Violations (FDA-483, Warning Letters…)
- Recalls
- Civil money penalties
- Seizure
- Injunction
- Prosecution

References

1. *Fundamentals of US Regulatory Affairs*, RAPS, 2005
2. 21 CFR Part 210, 21 CFR Part 211
3. *Pharmaceutical Quality System Q10*, ICH, May 2007.
4. *ICH Harmonised Tripartite Guideline Good Manufacturing Practice guide for Active Pharmaceutical Ingredients Q7* , ICH, November 2000
5. *Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations,* FDA, September 2006.
6. *A Risk-Based Approach to cGMPs*, FDA, October 16, 2002.
7. cGMP Amendment: http://www.fda.gov/cber/rules/amendcgmpfinal.pdf

Glisland Integral Solutions for Regulatory Affairs

- Regulatory compliance training
- Equipment/software validation
- Quality management system (GLP, GCP, GMP, QSR)
- Internal audit
- Risk analysis
- Regulatory submissions
- Custom software development

Contact Information

Glisland, Inc.

2059 Camden Ave, #299

San Jose, CA 95124

Phone: (408) 796-1883

Email: info@glisland.com

Website: http://www.glisland.com