FDA GMP Initiatives: Impact on CMC Reviews/Reviewers

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GMP Initiatives: Main Themes

- Integrating Review and Inspection functions
- Fostering scientific innovation to achieve a desired state of pharmaceutical manufacturing
- Establishing a Quality System in FDA

Initiatives Affecting CMC Reviewers/Reviews

- Review of drug cGMP Warning Letters by Center
- Establish a GMP technical dispute resolution process
- Include product specialists in PAI and GMP inspection; on-site data review
- Establish pharmaceutical inspectorates
- Allow manufacturing changes without prior approval by FDA

Warning Letters

- Review of GMP warning letters by CDER
- Consultation to CMC reviewers on scientific and technical issues
  - Criteria
  - Procedure

Dispute Resolution

- Current process for scientific disputes: CDER/CBER Guidance: Formal Dispute Resolution: Appeals Above the Division Level (Feb. 2000)
- Additional process for scientific and technical issues that arise as the result of GMP and PAI inspections
  - Tier one: Dispute resolution process at the District and Center level
  - Tier two: Dispute resolution at FDA panel
  - CMC Reviewers' involvement expected

Including Product Specialists in Inspections: Current System

- CMC Reviewers participation, informal, and selectively
  - Pre-Approval Inspections
    - Enhanced the science of inspection
    - Reduced the number of 483 observations and CMC review deficiencies
    - Shortened the CMC review time
    - Reduced the # of CMC review cycles
    - Positive feedback from industry
  - For cause inspections
    - Facilitated the finding of route causes of the regulatory concerns

Including Product Specialists in Inspections: Future Process

- Prior Approval, GMP and For-Cause inspections
  - On-site, or
  - On-call
- CMC reviewers and other product specialists
  - Formal and routine process

Trainings

- Pharmaceutical Inspectorate: Specific curriculums for investigators to conduct pharmaceutical inspections
- CMC reviewers and other product specialists
  - Risk-based regulatory paradigm
  - Industry residence program
  - Industry sponsored GMP training for reviewers
- Joint training on novel technologies, e.g.,
  - Process Analytical Technology

Changes without Prior Approval

- Comparability protocol guidance (draft)
  - Issued in Feb., 2003
  - Chemical drugs
  - Recommendations on preparing and using comparability protocols for post-approval changes
  - General principles and procedures associated with developing and submitting a comparability protocol
- ACPS Manufacturing Subcommittee
  - Discussion in the fall of 2003

What is a Comparability Protocol?

- A well-defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product

Comparability Protocol: Filing Mechanisms

- Protocols
  - Submission is optional
  - Part of original NDA or ANDA submission, or
  - Prior Approval Supplement
- Implementation of manufacturing changes
  - CBE-30, or
  - CBE-0, or
  - AR

Comparability Protocol: Types of CMC Changes

- Cover many dosage forms not covered under SUPAC Guidances
- Cover classes of chemical substances not covered under BACPAC Guidance
- Cover changes (single or multiple) not described in SUPAC, BACPAC and Changes to an Approved NDA and ANDA Guidances

Comparability Protocol: Basic Elements

- Description of the manufacturing change(s)
- Specific tests and study(ies) to be performed
- Analytical procedures to be used
- Acceptance criteria
- Data to be reported under or included with the comparability protocol
- Proposed reporting category for implementing the change(s)
- Action when equivalence not demonstrated using the approved comparability protocol
- Commitment

Comparability Protocol: Benefits

- Allowing FDA and industry to agree early on specified CMC changes, plan for assessing the effect of these changes and the reporting category - **Predictability**
- Savings in time of implementation and resources for many types of changes

Comparability Protocols: Implementation

- A new regulatory mechanism, therefore, FDA and industry experiencing a learning curve
  - ONDC established internal process to assure review consistency
- Guidance is hoped to foster innovation in manufacturing improvement, e.g.,
  - Making implementing PAT easier

Changes without Prior Approval Other Factors to be Explored

- Adequate pharmaceutical development work
  - Understanding the process and the product
  - Critical variables and quality attributes identified and controlled
  - Sharing Scientific information with FDA
- Right quality systems in place, e.g.,
  - Good changes control system
- Drugs considered low risk with respect to quality

GMP Initiatives: Long Term Benefits

- Integration CMC review and inspection functions
  - Close communication between Centers and Field Offices
  - Science- and risk-based CMC review and inspection
- Quality system at FDA and in industry
  - More efficient use of resources
  - More adaptable to innovation and changes
  - Improving product quality and public health need

Success will Require Efforts from both Industry and FDA