Supplements and Other Changes to an Approved Application

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Need for a New Approach to Approve and Implement Post Approval Changes

- Regulatory workload for industry and FDA
  - 20-30 post-approval supplements over the lifecycle of a generic product
  - 3,846 supplements filed to Office of Generic Drugs in 2006
- Ability to implement change
  - Typical CMC PAS review time: 9-18 months
  - Timeline from development to approval: 1-4 years
- Assure availability of high quality - low cost drugs to consumers
  - Encourage innovation
  - Prevent drug shortages

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What Drives the Generic Industry to Submit Post Approval Changes?

- Changes brought about by raw material suppliers
  - Discontinuation of the drug substance
  - Product moved to a new manufacturing site
  - Manufacturing process change
- Manufacturing changes
  - Process improvement
  - New equipment
  - Facility consolidation, expansion or relocation
  - Alternate raw material, drug substance and packaging material sources
- Compendia changes and upgrades to analytical methodology
- Outsourcing

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Current Regulatory Framework for Notification of CMC Changes

- Prior Approval Supplements
  - Regulatory pathway that provides FDA the ability to perform a scientific assessment that the proposed change will not have an adverse effect on drug safety and efficacy
- CBE-30 and CBE-0 Supplements
  - FDA reviews each of these submissions after the sponsor has implemented the change
  - Sponsor may be requested to perform additional studies or provide additional data to support the change
  - Applicability of the filing category may be clarified prior to submission
- Annual Reports
- Is this the most efficient means to utilize FDA resources to review CMC changes?

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What could a Risk-Based Post-Approval CMC Change Process Look Like?

- Maintain the current evaluation criteria
  - Does the change have the potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug product?
- *Major changes*
  - Require **Prior Approval** by FDA before implementation
    - e.g., new facility, new process, new API supplier
- *Moderate changes*
  - Utilize company's internal CMC Quality Systems to qualify the change
  - Report change to FDA at time of implementation
- *Minor changes*
  - Report annually (current process)

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CMC Quality Systems

- Model CMC Quality System structure after 21CFR820 Quality System Regulation
  - Subparts B, D-K most applicable
- Most elements of CMC Quality System structure are already in place to implement post approval change regulation
  - Quality system procedures
  - Organizational structure
  - Document controls
  - IQ/OQ/PQ
  - Equipment, process and method validation procedures
  - Change control procedure
  - CAPA

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NDA / ANDA Changes Guidance

- Re-issue to provide greater specificity of *major changes* that would require FDA approval prior to implementation
  - e.g., changes to rubber stopper formulations are not well addressed in current guidance
- Develop a decision tree to provide sponsors a framework to determine if the change can be qualified using internal CMC Quality Systems
- Submission of change in the following annual report submission

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Can the System Work?

- Requires awareness of company's senior management to CMC changes
- Inspection of the CMC Quality System would become part of FDA's routine GMP inspection process
- Would require Office of Regulatory Affairs to partner in new approach
- Pressure test proposal against existing data
  - Evaluate history of changes being effected supplements that were determined non-approvable or could not be implemented

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Opportunities to Reduce the Supplements through a CMC Quality System Approach

- Under current rules-based prescriptive approach, CBE-30 supplements could be eliminated for:
  - Manufacturing changes to companion applications after approval of the lead supplement
  - A change in a drug substance or drug product manufacturing process that reduces levels of bi-products and impurities
  - A move to an alternate testing laboratory within a company or externally
  - A move to an alternate solid dosage form packaging site within a company or externally
  - A new analytical method that provides greater assurance of product quality
  - Addition of specifications to comply with global compendia
  - Adjustment in the operating parameters of a terminal sterilization process within the approved Fo range

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Additional Opportunities to Reduce the Regulatory Burden

- Under current rules-based prescriptive approach, prior approval supplements may no longer be necessary to approve:
  - Addition of a new drug substance supplier previously approved in an existing application with the same dosage form
  - Minor changes in the size or shape of a container for a sterile drug substance or drug product
  - Adjustment of in-process specifications based on manufacturing history
  - Deletion of a non-compendia test after appropriate product history

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General Comments: CMC Quality System Risk-Based Approach

- Regulatory burden to effect the change projected to remain the same as current prescriptive approach
- Drug safety and efficacy would not be jeopardized
  - Future approach would utilize effective manufacturing Quality Systems that are currently in place
- Agency could focus resources on change that has the greatest potential to impact product quality
- Anticipated to minimally increase scope of CGMP inspections
- Would provide for faster implementation of change

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General Comments: CMC Quality System Risk-Based Approach

- Incorporates Quality by Design principles
  - Generic manufacturers generally hold broad production experience across multiple products manufactured in the same or similar manner
- Adaptive to wide differences in manufacturing processes and equipment
- Responsive to the changes in technology and industry practices
- Unlikely generic industry would implement CMC-related risk management strategies
  - Continuous process development post product launch not the practice

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Thank You

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