Managing the Product Lifecycle Continuum through Post-approval Change Management Plans: An Industry Perspective

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CASSS CMC Strategy Forum
January 25, 2016
Post-approval change management is difficult for global products, but utilizing globally pre-approved change management plans could make it easier for both industry and regulators to manage changes.

- Complexity of global filings
- Need for post-approval changes
- Post-approval change management protocols
- Example change
- Ideal state
Reasons for Global Complexity

• Desire to have rapid approval in all countries can result in different conditions approved
  • Changes, especially to tighten controls or specifications, occur during regulatory reviews
• Initial applications typically have limited manufacturing experience, e.g. they may not have the ultimate desired process or manufacturing network
• Planning for post-approval changes begins before submission of the initial marketing application
• Requirements for making changes (e.g. stability, PV matrix) are not uniform across all regulatory agencies
End Result: A Complex Set of Customized Global Dossiers that are Challenging to Maintain
Reasons for Post-approval Changes

Needed
- Supplier Change
- Pharmacopeia Update
- Regulatory Commitment
- CAPA

Wanted
- New Manufacturing Site
- New Equipment
- Process Improvement
- Change in Control Strategy
Global Supply Chain

- Drug Substance
- Drug Product
- Labeling/Packaging
- Distribution
- Patient
Country Specific Supply Chain

- Drug Substance
- Drug Product
- Labeling/Packaging
- Distribution
- Patient
Managing Post-Approval Changes

**US**
- File comparability protocol with BLA or as prior-approval supplement
- Get at least one level of filing relief
  - PAS to CBE
  - CBE to AR

**EU**
- File as Change Management Protocols Type II Variation, submit results in Type IB
- For specific, planned change

**Other Markets**
- No defined pathway for PACMP
- Differing data requirements
  - Stability Requirements
  - Process Validation Matrix
Advantages and Disadvantages of PACMPs

**Advantages**
- Regulatory certainty in US and EU
- Quicker implementation in US and EU

**Disadvantages**
- Additional time and resources to prepare and manage PACMP submission
- US and EU regulators don’t typically allow PACMPs to be broadly applicable
- No pathway outside US and EU
- No certainty protocol design will be acceptable in other markets
  - Uncertainty in timelines and data requirements
  - May need additional PV runs
Example Post-approval Change
Drug Substance Process Improvement

Data needed to support change

• Supportive development data
  • Lab data to support ranges
  • Viral clearance
  • Resin lifetime

• DS process validation runs
  • How many?
  • At each DS manufacturing site?
  • At center points or edges of control parameters?

• DS Stability Data
  • How much?
  • At each DS manufacturing site?

• DP Process Validation Runs
  • Necessary?
  • How many runs?
  • At each DP site?
  • From each DS site?

• DP Stability
  • At commercial scale?
  • How much?
  • At each DP site?
  • From each DS site?
Complexity of the Post-approval Change Global Submissions

- PACMP can answer data requirement questions for US and EU submissions
- For global roll-out customization may be needed for
  - Additional stability data
  - Difference in specifications
  - Difference in detail in change control sections
  - Country specific supply chain
  - Additional PV runs
- Global customizations can be resource intensive
- Global filings and approvals can take up to 5 years
  - Delays implementation of improvements
  - Causes complexity in dossier as changes have to be filed as alternatives to original process
Ideal State for Post Approval Changes

- Marketing authorizations describe change management system and includes generic protocols for how changes will be evaluated
- Change management system and generic protocols approved globally
- Changes executed against the pre-approved protocols could be implemented without prior submission
  - Managed through quality system
  - Do and tell submission
- Change management protocols should be updated as product or process knowledge is gained
Example of Generic Change Management Protocol

Change in Drug Substance Manufacturing Process (process improvement to site change)

- Number of PV runs required or rationale for how to decide
- Extended characterization data required
- Statistical methods for comparing data to current process
- Summary of procedure for investigating out-of-trend results
- Summary of continuous process monitoring
Cons and Cons of Including Change Management Protocols in Global Regulatory Filings

**Cons**
- Quality system inspected on capability to effectively evaluate changes
- Upfront commitment and planning of change plans
- Additional data needed in filing to support change plans

**Pros**
- Standardized requirements for change protocols across regulatory agencies
- Upfront agreement between sponsor and regulators on how change will be managed
- Less post-approval submissions needed prior to implementation
- Faster implementation of process improvements
Conclusions

• Post-approval change management is extremely complex for global products

• Changes may take 5 years to receive global approval which delays implementation of improvements and adds to supply chain complexity

• Post-approval change management protocols are an effective process to get up front agreement from agencies on the change protocol and can speed implementation

• Regulatory processes for PACMPs are currently well established in only US and EU

• An ideal state could have protocols submitted with the initial global marketing applications describing how changes will be evaluated so that improvements could be efficiently filed and implemented