Best Practices for Post Approval Changes

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History and Current Landscape for Post-Approval Changes

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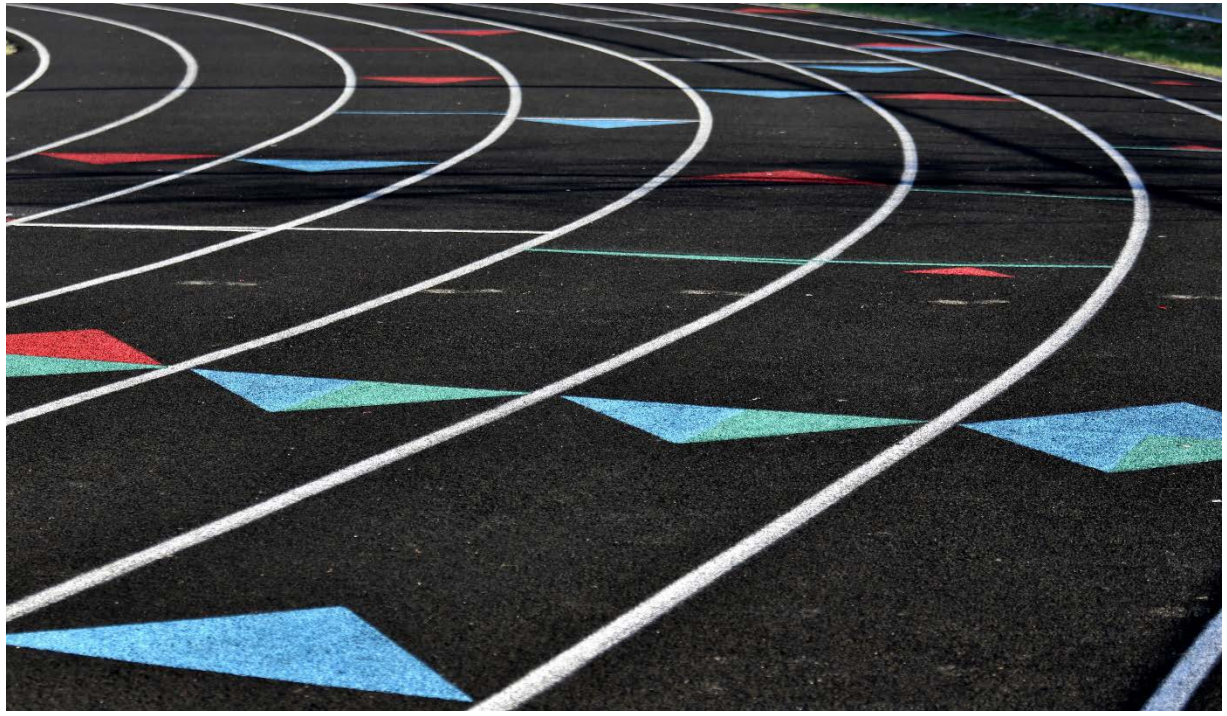
- **1995** - SUPAC-IR
- **1997** - SUPAC-IR & ANSWERS
- **1997** - SUPAC-MR
- **1997** - SUPAC-SS
- **1998** - PAC-ATL (PA CHANGES TO ANALYTICAL TESTING LABORATORY SITES)
- **2004** - CHANGES TO APPROVED NDAS & ANDAS
- **2014** - CMC POST-APPROVAL CHANGES DOCUMENTED IN ANNUAL REPORTS
- **2018** - POST- APPROVAL CHANGES TO DRUG SUBSTANCES

- ✓ 21 CFR 314.70 requires FDA notification of changes.
- ✓ Drugs have increased in complexity
- ✓ Additional regulatory roadmaps can be beneficial when it comes to post-approval changes for these products.



Filing Requirements of Complex Generic Post Approval Changes

Guidance on Data Requirements for certain changes to complex drug or combination products can be helpful.

Filing Categories	Examples of Types of Changes	Potential Data Requirements
PAS CBE-30 CBE-0 AR	Formulation Changes Batch Scale Up Site Transfers Packaging Changes Excipient Source Changes	Number of Batches? Stability required? In-vivo/In-vitro BE Requirements? Characterization Data?

Challenges - Life Cycle Management of Complex Products

Complex generic products often have a multi-layered structure or complex manufacturing processes. This complexity makes it challenging to assess the impact of changes on product quality, safety, and effectiveness.

- Although resources are available to guide drug development / approval for complex products (e.g., Product Specific Guidances, Controlled Correspondence, Product Development Meetings, Pre-submission Meetings), additional resources can be helpful for post approval changes to complex products.
- Controlled correspondences does not address urgent changes commonly encountered with routine manufacture of drug products while waiting a minimum of 60-120 days for a response.

TAKEAWAY: The Agency has done a commendable job issuing guidance and providing avenues for scientific discussion in support of drug development to bring complex generics to market – however – guidance on complex products and changes can be helpful to avoid overly conservative filing approaches to post-approval changes.

Case Study–DP Manufacturing Site Change

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Complex Peptide
Sterile Injectable

- **Proposed Change:** Site change for manufacture of drug product
- **Submission Type:** CBE-30/PAS
- **Submission Requirements#:**
  - Specifications
  - Methods
  - Master Batch records
  - Sterility Assurance Package
  - Process controls
  - CoAs and batch records
  - Stability data

not all inclusive

Uncertainties

- Will one batch per strength suffice for a complex peptide product?
- Immunogenicity data required?
  - 3 batches required?
  - End of shelf-life immunogenicity required ?
- Repeat physicochemical characterization?
  - all characterization tests be required – or - only a subset – and - which ones ?

TAKEAWAY

Additional guidance / recommendations would be beneficial as more complex products are approved.

Controlled correspondence allows for mechanism of feedback from the Agency - however - additional guidance and mechanisms for seeking feedback would also be beneficial in navigating such changes.

Best Practices

- ✓ Use regulations and guidance documents (when available) to determine the appropriate reporting category for the change and provide sufficient supporting data.
- ✓ If there are multiple related changes, the most restrictive filing category would apply.
- ✓ If guidance is not available for changes to complex generics, or there are unique considerations at hand, utilize Controlled Correspondence to obtain FDA concurrence prior to submission.
- ✓ Clearly list all proposed changes in the cover letter.
- ✓ In situations where there could be a supply disruption, contact FDA's drug shortage group.
- ✓ Keep track of USP updates.
- ✓ Work with your DMF holder closely (as applicable).

Parting Thoughts & Opportunities

- ✓ While the landscape for post-approval changes has remained largely unchanged over the years, generic products continue to advance in complexity.
- ✓ Challenges associated with post-approval changes for complex generic products is related to their unique characteristics, regulatory uncertainties & the need for extensive data.
- ✓ Additional post-approval guidance could allow for new avenues to be available for scientific discussion related to complex post-approval changes.
- ✓ Success requires careful planning, collaboration and effort from both FDA and Industry ultimately resulting in:

Reduced Cost and Time

↓

Reduced Regulatory Burden

↓

Reduced Drug Shortages

Thank you!

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