Life Cycle Based Approach: Life Cycle Based Approach: 
Process Change Requirements

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CMC Supplements

CMC => lifelong commitment

FFDCA and 21 CFR 514.8 => allow (A)NADA holders to make post-approval CMC changes

The Modernization Act of 1997 => provides requirements for making and reporting manufacturing changes to an approved application.

GFI 83: Chemistry, Manufacturing and Controls:
Changes to an Approved (A)NADA

- Components and composition
- Manufacturing sites
- Manufacturing process
- Specifications
- Container closure system
- Miscellaneous changes
- Multiple related changes

Bulk of workload at HFV-140 => Post Approval Supplements
ALTERNATE ANALYTICAL LABORATORY FOR TESTING RAW MATERIALS
DOSAGE FORM CHANGE
PROVIDE FOR AN ADDITIONAL MANUFACTURER OF DRUG SUBSTANCE
CHANGE IN STABILITY TEST SITE
REVISED STABILITY COMMITMENT AND REMOVAL OF HARDNESS FOR STABILITY TESTING
CHANGES TO THE EXCIPIENT
ADDITION OF A NEW SOURCE OF DRUG SUBSTANCE
UPDATED LABELING FOR DRUG SUBSTANCE

Reporting Post-Approval Changes

1) Major Change (Prior Approval Supplement, PAS)

2) Moderate Change (Supplement - Changes Being Effected)
   - CBE-30
   - CBE-0

3) Minor Change (Annual Report, MCSR)

Prior Approval Supplement (PAS)
- X-xxxxxx-C-xxxx-CP
  - Must be clearly labeled as Prior Approval Supplement
  - Change can not be implemented until it is approved by CVM
  - 120 days for review (pioneer)
  - 270 days for review (Generic by 2013)
Reporting Post-Approval Changes

CBE-30  X-xxxxx-C-xxxx-CS

- Must be labeled as a Supplement-Changes Being Effected in 30 Days
- Change to be implemented in 30 days
- CVM must accept submission as a CBE-30 before review

Reporting Post-Approval Changes

CBE-30  If not accepted as CBE-30, reclassified as Prior Approval Supplement (letter issued within 30 days of receipt)

- 120 days for review (pioneer), 270 days for review (Generic by 2013)

Reporting Post-Approval Changes

CBE-0  X-xxxxx-C-xxxx-CI

- Must be clearly labeled as Supplement-Changes Being Effected
- Change to be implemented immediately
- 120 days for review (pioneer)
- 270 days for review (Generic by 2013)
### Reporting Post-Approval Changes

**Minor Changes & Stability Report (MCSR)**

- Must be clearly labeled as *Minor Changes and Stability Report*
- Change implemented immediately (often before report is submitted)
- Includes updated stability data

### Manufacturing sites

<table>
<thead>
<tr>
<th>Major Change</th>
<th>Moderate Change</th>
<th>Minor Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS</td>
<td>CBE-30</td>
<td>CBE-0</td>
</tr>
<tr>
<td>Move to diff. site</td>
<td>Move to diff.</td>
<td>Move to diff.</td>
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<tr>
<td>never inspected by</td>
<td>site for testing</td>
<td>site for manuf. or processing</td>
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<tr>
<td>FDA</td>
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</tr>
<tr>
<td>procedures approved</td>
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</tr>
<tr>
<td>in the application</td>
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<td></td>
<td>Move to diff.</td>
<td>Move to diff.</td>
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<tr>
<td></td>
<td>site for manuf.</td>
<td>site for</td>
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<tr>
<td></td>
<td>site for</td>
<td>secondary</td>
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<tr>
<td></td>
<td>manuf. or</td>
<td>packaging &amp;</td>
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<tr>
<td></td>
<td>processing</td>
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<tr>
<td></td>
<td>final</td>
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<tr>
<td></td>
<td>intermediate.</td>
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</tbody>
</table>

### Container closure system

- Change that may affect drug product sterility assurance e.g., glass ampule to glass vial with elastomeric closure
- Changes in size/shape of sterile drug container
- Changes in size/shape of non-sterile drug container

### Components/composition

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<tbody>
<tr>
<td>PAS</td>
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<td>CBE-0</td>
</tr>
<tr>
<td>Formulation change</td>
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<tr>
<td></td>
<td></td>
<td>ingredient</td>
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<td></td>
<td></td>
<td>color only</td>
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### Manufacturing process

- Fundamental change in manuf. process e.g., dry to wet granulation or vice versa.
- Change in method or controls that provide increased assurance in critical quality attributes
- Change in equipment of same design & operating principle.
### Sponsor Responsibilities Regarding Master Files (MF)

- Update CVM regarding current suppliers of drug substance
- Notify CVM/FDA of any and all changes in a MF reported by VMF/DMF holders through a submission to the (A)NADA or (J)INAD with a reference to the MF and a LOA
  - At a minimum, annually reference each MF that is approved in the (A)NADA, since the MF should be updated annually by the MF holder if not more often.
  - Notify CVM/FDA of any MF that is no longer actively used
  - Submit an amendment to applications when the MF is amended or updated, including responses to deficiency letters by the MF holder
- Notify suppliers (MF holders) of changes such as company name and address change, particularly when a new letter of authorization (LOA) will be required

### Labeling Changes in CMC Supplements

- If the CMC change directly impacts the labeling (e.g., the manufacturing facility is listed on the label, and the sponsor submits a CMC supplement for approval of a new manufacturing facility), then updated labeling should be included in the CMC supplement
- DMT will consult the label to the appropriate TAD for review.
- If the label is not acceptable, the CMC supplement will be incomplete.
- When the CMC supplement is approved, the submitted labeling is also approved. If facsimile labeling was submitted in the CMC supplement, once the label is approved the sponsor should send the final printed labeling to the appropriate TAD, not to DMT.

### Specifications

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<td>relax</td>
<td>addition to spec. that provides increased assurance</td>
<td>tightening of acceptance criterion</td>
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- Labeling Changes in CMC Supplements
- Specifications

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Labeling Changes in CMC Supplements

- Labeling should only be included in CMC supplement if it needs to be there.
- Labeling should never be included in Annual Reports.
- If a label is included in the CMC supplement, the label change may determine the type of supplement (CBE-30 vs Prior approval). If the label change requires prior approval, the supplement is prior approval even if the CMC information could be submitted as a CBE or CBE-30.

Labeling Changes in CMC Supplements

- If a labeling change is included in a CBE-30, the TAD will be involved in the decision on whether the supplement is acceptable as a CBE-30 or needs to be reclassified as prior-approval.
- If sponsors have questions about whether labeling should be included in their CMC supplement or what category of supplement to submit, the sponsor should contact CVM.

References

- GFI 83: Chemistry, Manufacturing and Controls Changes to an Approved NADA or ANADA
- GFI: SUPAC (Scale-up Post Approval Changes) Immediate Release and Modified Release Solid Oral Dosage Forms
Thank You!

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