Post Approval Regulatory Consideration for Changes to Manufacturing Process and Facilities

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Process Validation

- Stage 1-Process Design

  The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

- Stage 2- Process Qualification

  During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

- Stage 3- Continued Process Verification

  On going assurance is gained during routine production that the process is operating in a state of control.

Stage 3-Continued Process validation

- §211.180 (e) and §601.12
  - Evaluate the performance of the process by collecting and analyzing product and process data that are related to product quality
  - Identify problems and determine whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control
- §314.70 and section of 506A of FD&C Act
  - Reporting on Postapproval changes

Guidances Related to Post-Approval Changes

1. Changes to an Approved NDA or ANDA
2. Reportable CMC Changes for Approved Drug and Biological Products
3. CMC Postapproval Manufacturing Changes to Be Documented in Annual Reports
4. CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports
5. SUPAC Guidances
   - SUPAC-IR, SUPAC-MR, SUPAC-SS, SUPAC-manufacturing Equipment Addendum 2014

Reporting Categories

1. Major Change
   - Prior Approval Supplement (PAS)(§314.70(b))
2. Moderate change
   - CBE30 (§314.70(c)(3))

   FDA may send email/letter within 30 days of receipt of the supplement if a PAS is indeed required for filing the proposed changes.

   - CBE0 (§314.70(c)(6))

   If disapproved, the manufacturer should cease distributing of the drug product made using the disapproved change (§314.70(c)(7))
3. Minor change
   - Annual Reportable (§314.70(d))

Type of Changes to Be Reported

1. Components and Composition
2. Manufacturing sites
3. Manufacturing process
4. Specifications
5. Container closure systems
6. Labeling
7. Miscellaneous changes
8. Multiple related changes

Type of Changes: Manufacturing Sites

1. A move to a different site (for a non-sterile product)

2. A move to a different area within the same site (for a non-sterile product)

3. Site change for sterile products

Definition of a Manufacturing Site

1. Drug product manufacturer
2. Drug substance manufacturer
3. Drug substance intermediate manufacturer
4. Testing site including sites for final release testing, in-process testing and/or stability testing
5. Packaging and labeling sites

Move To A Different Site (non-sterile products)

	Submission type
Have a previous acceptable Inspection history	CBE30
Do not have a previous satisfactory inspection history for type of operations being proposed	PAS
Never been inspected	PAS

However, based on the complexity, the reporting category could be different.

If it is a DS intermediate manufacturer, a CBE30 can be submitted.

Manufacture or process of in-process material with modified –release characteristics	Submission type
Modified-release solid oral dosage form	PAS
Depot drug products	PAS
Transdermal systems	PAS
Liposomal drug products	PAS
Oral /nasal metered-dose inhalers (MDIs)	PAS
Dry powder inhalers (DPIs)	PAS
Drug product with nasal spray pumps	PAS

Move To A Different Site (non-sterile products)-Continue

Even though the site has an acceptable compliance history, depending on the change, the reporting category could be different

Site already have the compliance history	Submission type
If it is a primary package for SODF including modified release products	CBE30
A move to a different testing site for approved testing	CBE30
Fulfill a post-approval commitment	CBE30

Site already have the compliance history	Submission type
A new site for secondary packaging	AR
A new Labeling site	AR
A new site for DS intermediates other than the final intermediate	AR
A new contract sterilization site for packaging components	AR
A new site for the ink imprinting of SODF	AR

Move To A Different Site / Area (sterile products)

Move to a different site	Submission type
Aseptically processed sterile DS or DP manufacturing (SVS, SVL)	PAS
DP with terminal sterilization process (SVT)-first time*	PAS

* Once the SVT in the new site is approved, subsequent supplements can be submitted as CBE30.

Move to a new constructed building or area within an existing facility		Submission type
Aseptically processed sterile DP	Have similar approved products with the same filling line	CBE30
	change the container types and size	PAS
DP with terminal sterilization process (SVT)	do not have an approved SVT products	PAS
	have FDA approved SVT products	AR

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Type of Changes: Manufacturing Process

1. Changes for a non-sterile product

2. Change for a sterile product
   - ✓ Changes that may affect sterility assurance
   - ✓ Changes related to equipment

Changes in Manufacturing Process (non-sterile products)

Changes in Manufacturing Process	Submissions
Changes that may affect the controlled release, metering or other characteristics of the dose delivery	PAS
Fundamental change in DP/DS manufacturing process	PAS
Any process change made after the final intermediate processing step in DS manufacture	PAS
Addition of an ink code imprint or change to a new ink that never been approved	PAS
Addition of an ink code imprint or change to a new ink that has been used in an approved DP	AR
Establishing a new procedure for reprocessing	PAS
Change in the synthesis or manufacture of the DS	PAS
Change in production scale (need to check SUPAC)	CBE30*
A change in methods or controls that provides increased assurance	CBE0
Replacing of equipment with the same design	AR

Changes in Manufacturing Process (sterile products)

PAS: any changes that may affect sterility assurance

- Changing in the sterilization method
- Addition, deletion, or substitution of sterilization steps/procedures for handling sterile materials
- Changing from bioburden-based terminal sterilization to the use of an overkill process, and vice versa
- Changing to aseptic processing methods, including scales or extend total processing time by MT 50% beyond the validated limits in the approved application
- Changing in sterilizer load configurations that are outside the validated loads
- Changes in materials or pore size rating of a filter

Changes in Manufacturing Process (sterile products)

PAS: Related to equipment

- Replacing sterilizer with different operation principle
- Addition of a new aseptic processing line made with different materials
- Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling
- Replacing or addition of lyophilization equipment

Changes in Manufacturing Process

- For a natural product
  - ✓ Changes in the virus or adventitious agent removal or inactivation method
  - ✓ Changes in the source material (e.g. microorganism, plant) or cell line
  - ✓ Establishment of a new master cell bank or seeds
- A PAS should be submitted

Examples of Reporting Categories - Changes in Manufacturing Process

- A firm submitted a PAS for changes made on the DP manufacturing from wet granulation to a dry granulation
  - ✓ True

- A firm submitted a CBE30 for changing the drying process from fluid bed to oven dry with trays, for a tablet
  - ✓ False (should be a PAS)

- A firm submitted a CBE0 for changing an existing code imprint from a numeric to alphanumeric code
  - ✓ Can be a AR

Examples of Reporting categories

Changes in Manufacturing Process for a Sterile Product

- A firm made a change on the filtration parameters for aseptic process including flow rate, pressure, time or volume
  - ✓ CBE30

- A firm made a change on the filter materials or pore size rating
  - ✓ PAS

- A firm is eliminating in-process filtration performed as part of the terminally sterilized drug product
  - ✓ CBE0 *

Reporting Category For A Code Imprint

- Addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form
  - ✓ PAS
- Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage form **other than** a modified-release dosage form
  - ✓ AR
- Addition of an ink code imprint or change to or in the ink used for an existing imprint code **-if the ink as changed is not currently used on CDER-approved drug product**
  - ✓ PAS

Case Study #1: Reporting Category

- A firm submitted a CBE30 for moving the packaging line to a new site for a tablet product. During the supplement review, it was found that
  - in addition to the bottle package, the firm added the blister package
  - the new site has never been approved for the blister package production

- Do you think a CBE30 is appropriate for reporting the change?
- **Answer: No, CBE30 is denied to a PAS**

Case Study #2: Reporting Category

- A firm submitted a CBE30 for moving the release testing of a sterile product to a new site that has been inspected by Agency. While reviewing the inspection history of a new site, we noticed that
  - the new site has only been approved for chemical testing (LCP)
  - the release test for the current product includes microbiological testing (LMN) and sterility testing (LMS), and were not covered during the previous inspections.

- Do you think a CBE30 is appropriate for reporting the change?
- **Answer: CBE 30 is denied to a PAS**

Case Study #3: Review the Changes

- Due to a new OAI status on the testing site, the applicant submitted a CBE30 to move the XRPD testing to another contract testing site. The contract testing site has been inspected for conducting the chemical testing. During the review, we noticed that
  - the new site has never performed XRPD testing
  - A call to the new site confirmed that there is no equipment on site to perform the test

- The supplement is put into withhold.
- **Take home message**: It is the applicant's responsibility to check if the new site has the capability of conducting the test or if the new site is ready for the test.

Challenge Question #1

- What reporting category the sponsor should use if a lyophilized drug product is moved to a new site, and
  a. the new site has never been inspected by Agency
  b. the new site has no previously approved lyophilized products
  c. the new site has previously approved to manufacture lyophilized drug products but with a different container type and/ or size.

Answer: PAS for all three

Challenge Question #2

- What reporting category the sponsor should use if the sponsor is replacing an existing wet granulator to:
  a. a different model with different design that does not affect the process methodology or process operating parameters
  b. the exact same model

- Answer: a-CBE30 b-AR

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Questions?

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