Managing Quality Post-Approval Supplements: Quality-Related Changes

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Learning Objectives

- Understand Reporting Categories for Post Approval Submissions
- Avoid Common Deficiencies
- Describe recent GDUFA III Updates for Prior Approval Supplements

Common ANDA Post-Approval Quality Changes

- Drug substance
  - sites change, new drug substance sources, processes, equipment, specifications, analytical procedures
- Drug Product
  - formulations (new strengths, excipients), sites, processes, equipment, batch sizes, IPC, specifications, analytical procedures, shelf life
- Container closure system
  - components, suppliers, size/shape, resins/colorants, packaging configurations
- Testing facilities / packaging facilities

Common Causes for CRs

- API source/API process (DMF changes)
- Widen specifications (impurity, dissolution)
- DP site
- Container closure

Risk-based Reporting Categories

Major Changes

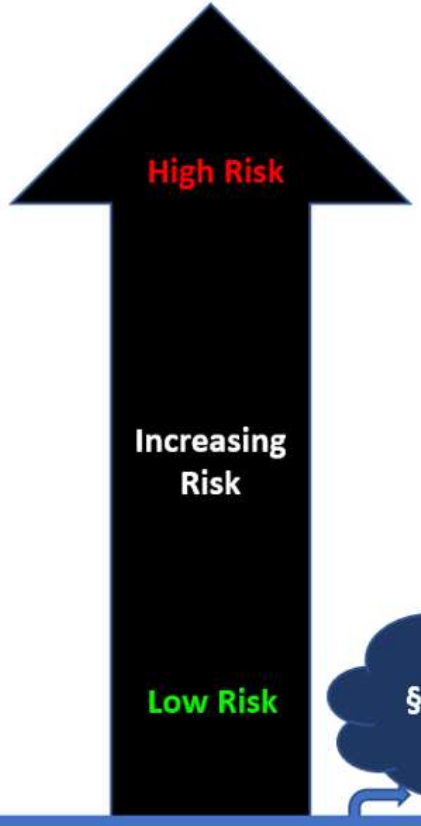
- PAS: Implement change after FDA approval

Moderate Changes

- CBE-0: Implement change immediately after supplement receipt at FDA
- CBE-30: Implement change 30 days following supplement receipt at FDA

Minor Changes

- Annual Report (AR): Notification after implementation



§§ 314.70(b)-(d)

Substantial (PAS), **moderate (CBE-0/30)**, or **minimal (AR)** **potential to have an adverse effect** on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product

Examples of AR Changes

1. Elimination or reduction of an overage from the drug product manufacturing batch formula that was previously used to compensate for manufacturing losses.
2. Extensions of drug product expiry based on an approved stability protocol.
3. Any change made to comply with the official compendium, except relaxation of an acceptance criterion or deletion of a test.

Examples of AR Changes (…contd.)

4. Change in the supplier of an excipient, where the technical grade and specification for the excipient remain the same.
5. A change in the order of addition of ingredients for solution dosage forms.
6. Tightening of acceptance criteria.

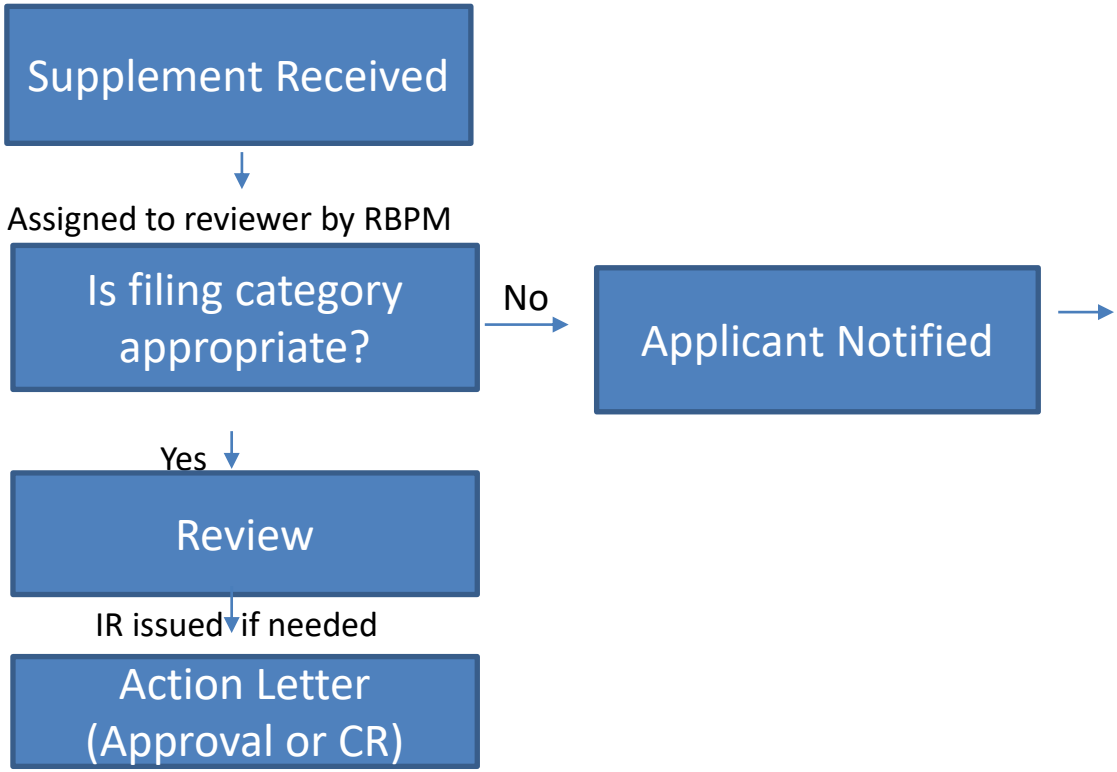
Examples of PAS Changes

1. Addition of a new API supplier
2. Change in the route of synthesis of drug substance
3. Relaxing acceptance criteria to accommodate failing data (e.g., impurity levels) or deleting tests (e.g., antimicrobial effectiveness testing)
4. Equipment of different operating principles (e.g., oven tray dryer vs. fluid bed dryer)

Examples of PAS Changes (…contd.)

5. Add new flavor or color
6. Adding a new strength
7. Sterile drug product- a change from a glass ampule to a glass vial with an elastomeric closure.

Supplement Review Process



* If CBE downgraded to AR, applicant told to withdraw supplement.
* If CBE elevated/denied to PAS, notification letter sent to applicant. Applicant resubmits as PAS.

*An applicant may ask FDA to **expedite** its PAS review for public health reasons (e.g., drug shortage, extraordinary hardships on applicant, etc.)

Common Reasons for CBE 0/30 Denials to PAS

- API process changes
- Drug Product manufacturing site changes
- Container closure changes
- Addition of sterile filling line
- Stability protocol changes

Tips to Submit Better Supplements & Avoid These Common Deficiencies

1. Use regulations and guidances to determine the appropriate reporting category for the change and provide sufficient supporting data (e.g., per SUPAC, Tablet scoring guidance's)

✓ Do not rely on data to justify classification, but instead justify reporting category based on cited guidance applicable sections and nature of proposed change(s). If multiple related changes, most restrictive filing category will apply.

✓ Clearly list **all** proposed changes in the cover letter.

2.Keep track of USP updates

3. Work with your DMF holder closely

Challenge Question #1

Applicant wants to add an additional API supplier to increase capacity for a drug shortage product. That change should be submitted as a?

A. PAS

B. CBE-30

C. PAS (expedited review requested)

D. CBE-0

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GDUFA III UPDATES

PRIOR APPROVAL SUPPLEMENTS (PAS)

GDUFA RELATED CHANGES

Learning Objectives

- Understand the goal dates for Prior Approval Supplements
- Benefits of using Cover Letter Attachment
- Describe types of Post Approval submissions accepted as a Controlled Correspondence

Learning Objectives

- When to submit a Post-Complete Response Letter (CRL) Clarification Teleconference
- What to consider when submitting a reclassification of Facility- Based Major CRL Amendment for PAS
- What qualifies for a Request for Reconsideration for Supplements

PRIOR APPROVAL SUPPLEMENTS (PAS)

Submission Type	Goal
Standard PASs	90% within 6 months of submission date if preapproval inspection not required.
	90% within 10 months of submission date if preapproval inspection required.
Priority PASs	90% within 4 months of submission date if preapproval inspection not required.
	90% within 8 months of submission date if preapproval inspection required and applicant meets requirements under section I(B)(2)(b).
	90% within 10 months of submission date if preapproval inspection required and applicant meets any limitations as described under section I(B)(2)(c)

PRIOR APPROVAL SUPPLEMENTS (PAS)

Submission Type	Goal
Standard PAS Major Amendments	90% within 6 months of submission date if preapproval inspection not required.
	90% within 10 months of submission date if preapproval inspection required.
Priority PAS Amendments	90% within 4 months of submission date if preapproval inspection not required.
	90% within 8 months of submission date if preapproval inspection required and applicant meets requirements under section I(B)(4)(b).
	90% within 10 months of submission date if preapproval inspection required and applicant meets any limitations as described under section I(B)(4)(c).
Standard and Priority Minor PAS Amendments	90% within 3 months of submission date.

COVER LETTER ATTACHMENT

- Cover Letter Attachments for Controlled Correspondences and ANDA Submissions – Guidance for Industry – December 2021
- Useful guide to help prepare cover letter and recommend attaching a completed Appendix C with new supplements, amendments to pending supplements, amendments to tentatively approved PEPFAR ANDAs, and correspondences related to these submissions

APPENDIX 3: COVER LETTER ATTACHMENT FOR SUPPLEMENTS TO APPROVED ANDAS, AMENDMENTS TO PENDING SUPPLEMENTS, AMENDMENTS TO TENTATIVELY APPROVED PEPFAR ANDAS, AND CORRESPONDENCE RELATED TO THESE SUBMISSIONS

ANDA background	
Abbreviated new drug application (ANDA) number	
Applicant	
Submission Date	
Email	
Established Name	
Dosage Form	
Strength(s)	
Reference Listed Drug (RLD) (proprietary name (brand name) and application number)	
Reference Standard (RS) (proprietary name (brand name), if any, established name, and application number)	
If priority review is being requested, please refer to FDA's Manual of Policies and Procedures (MAPP) 5240.3 (Rev. 5) *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*[12]	

Select all applicable information included in the submission			
☐ Administrative General Correspondence ☐ Scientific General Correspondence	☐ Bioequivalence	☐ Biopharmaceutics	☐ Clinical
☐ Drug Substance DMF #:	☐ Drug Product	☐ Labeling	☐ Microbiology
☐ Patent or Exclusivity	☐ Pharm/Tox	☐ Manufacturing: ☐ Facility ☐ Active Pharmaceutical Ingredient (API) ☐ Finished Dosage Form (FDF) (including packaging/labeling) ☐ Testing ☐ Other (e.g., storage warehouse, device constituent parts) ☐ Process	
☐ Notice of Commercial Marketing			

Additional background	Yes	No or N/A
1. Is the email secure? If no, apply for a secure email with the FDA by contacting secureemail@fda.hhs.gov.		
2. Was a Pre-Submission Facility Correspondence (PFC) submitted?		
3. If a PFC was submitted, have any changes been made to the pre-submitted facility information?		
4. Does the submission contain any technology that has been accepted into or may qualify for the Emerging Technology Program[13]?		
Drug-device combination product	**Yes**	**No or N/A**
5. Is the proposed product a drug-device combination product? If yes, answer questions #6 through #9.		
6. Does the supplement propose a change to the drug-device combination product that may impact quality or labeling"?		
7. Does the supplement propose a change to the drug-device combination product that may impact the user interface?		
8. Does the submission include comparative analyses for a drug-device combination product? If yes, then specify location in the submission:		
9. Does the submission include additional data and/or information, such as data from a comparative use human factors study, to support differences in user interface? If yes, then specify location(s) in the submission:		
Does the submission (supplement or amendment to the supplement) include any of the following?	**Yes**	**No or N/A**
10. New strength (including new fill volume for parenteral products)		
11. Modified formulation		
12. Specification change(s)		
13. New container closure system		
14. Request for an Rx-to-over the counter (OTC) switch		

15. A reactivation/reintroduction request as noted in MAPP 5200.7 (Rev. 1)[14]		
16. Revised and/or new patent certification and/or exclusivity statement		
17. Updated labeling due to a new or revised patent or exclusivity currently listed in the Orange Book		
18. A new facility that has never been inspected for similar operations to those proposed in the supplement		
19. Removal of a facility		
20. Active Pharmaceutical Ingredient (API) source change If yes, then include Drug Master File (DMF) #:		
21. A Pharmacology/Toxicology (safety) justification for example nonclinical studies as defined in 21 CFR 58.3(d) If yes, then specify justification/study type and location in the submission:		
22. New bioequivalence (BE) study/studies If yes, then specify the following for each new BE study: a. Select Study type: in vivo or in vitro, including failed study b. Study Number c. Study Site (clinical, analytical, in-vitro testing) Name and Address d. Location of new BE study in the submission		
23. An alternate method for demonstrating BE (e.g., modeling, in vitro testing) that deviates from the current recommendations in a Product-Specific Guidance		
24. A waiver request under 21 CFR 320.22? If yes, include the module where your waiver is located:		

Select one filing category corresponding to the highest risk of all proposed supplemental changes, ranked by supplement filing category (PAS, CBE-30, CBE-0) per 21 CFR 314.70		
☐ PAS	☐ CBE-30	☐ CBE-0

For Amendments Only			
Type of amendment	**Supplement #**	**Date of FDA correspondence or action that elicited the amendment (e.g., Complete Response Letter**	**Is this a response to a CRL?**

		(CRL), discipline review letter (DRL), information request (IR), or tentative approval (TA)):		
			Yes	No or N/A
Unsolicited				
Solicited				
President's Emergency Plan for AIDS Relief Program (PEPFAR) Post-TA[15]				

Proposed changes				
• For all supplemental changes proposed, populate the table below, ranked by supplement filing category (PAS, CBE-30, CBE-0) per 21 CFR 314.70				
#	Change description	Filing category	Scale-Up and Post Approval Changes (SUPAC) level (1, 2 or 3), as applicable[16]	Justification for filing category based on current guidances and/or risk assessment If the same change has been previously approved, include ANDA # and approval date for the same change.
1				
2				
3				
4				
5				

PAS SUBMISSION BASED ON AGENCY REQUEST

- AKA “CBE 0/30 denied to PAS”
- COVER LETTER
  - Include reference (date) of the communication between the Regulatory Business Process Manager, the name of the and the Applicant’s Point of contact

CONTROLLED CORRESPONDENCE

- Draft Guidance published in Dec 2022

1. Requesting information on a specific element of generic drug product development:

   a. Before ANDA submission;

   b. After a Product-Specific Guidance (PSG) Teleconference if a prospective applicant or applicant seeks further feedback from FDA;

   c. After issuance of a complete response letter (CRL) or tentative approval;

   d. After ANDA approval; or

2. Concerning postapproval submission requirements that are not covered by Center for Drug Evaluation and Research (CDER) postapproval changes guidance and are not specific to an ANDA.

Post-Complete Response Letter Clarification Teleconferences Between FDA and ANDA applicants

- Guidance published October 2022
- Clarify identified deficiencies
- Major and Minor deficiencies
- Questions requiring further agency review, disputes about classification of CRL, or new information submitted will not be addressed

Reclassification of Facility-Based Major CRL Amendments

- Upon submission of a Facility-Based Major CRL Amendment for a PAS, an applicant can request that FDA reclassify the Major Amendment to minor
- Must be made at time of amendment submission and include supporting information detailing why the facility deficiency has been resolved and no additional facility assessment is needed

Request for Reconsideration

- A pathway to handle FDA regulatory action that relates to a PAS and has scientific significance
- Examples of actions to PAS:

Refuse to receive decision
Tentative Approval letter
Complete Response letter
Classification of a major amendment
Classification of the standard review status
CBE 0/30 denied to a PAS

Challenge Question #2

Applicant was issued a CRL for a PAS which included the following MAJOR deficiencies; Drug product, Microbiology and Facilities. Which of the following pathways is appropriate for reconsideration/reclassification request from Major to Minor?

A. Controlled Correspondence

B. Post-CRL Teleconference

C. Request for Reconsideration

D. Reclassification of Facility-based Major CR Amendment


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