Post-Approval Change Management with sANDA Examples and Case Studies

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Outline

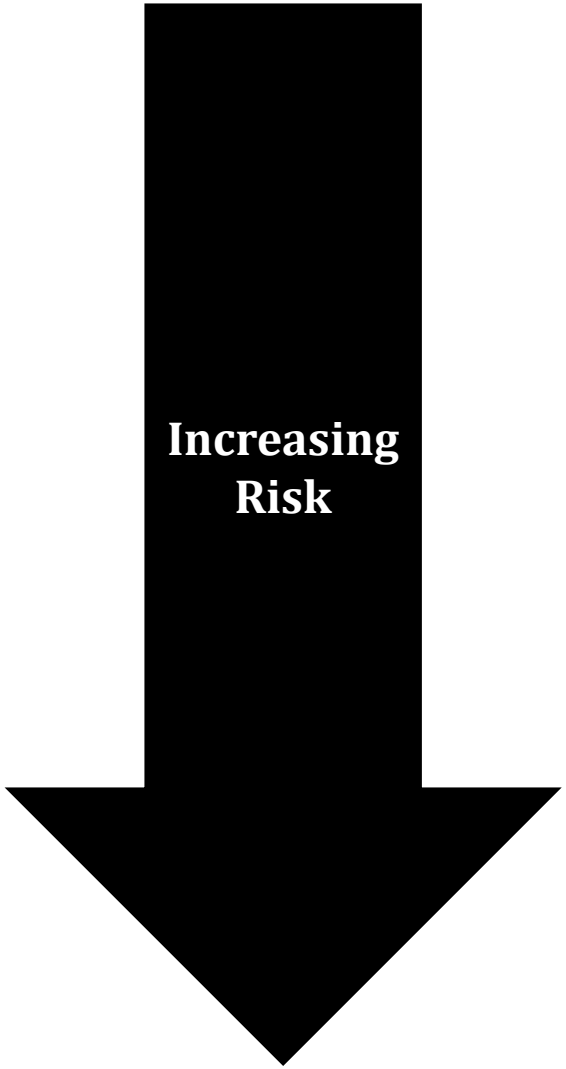
- Post-approval Changes - Regulations and Guidances
- Risk-based reporting categories
- Supplement review process overview
- Examples & Case Studies
- Common deficiencies in supplements and how to avoid them

Post-Approval Change Regulations

- 21 CFR 314.70 - Supplements and other changes to an approved application.
- 314.70(a)(1)(i): …the applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully.
- 314(a)(2): The holder of an approved application…must assess the effects of the change before distributing a drug product made with a manufacturing change.

Risk-based Reporting Categories

- Minor Changes
  - Annual Report: Notification after implementation
- Moderate Changes
  - CBE-0: Implement change immediately after supplement receipt at FDA
  - CBE-30: Implement change 30 days following supplement receipt at FDA
- Major Changes
  - PAS: Implement change after FDA approval



Post-Approval Change Regulations

- Prior Approval Supplement (PAS) – 21 CFR 314.70(b)
  - A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a **substantial potential** to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.
- Changes Being Effected (CBE/CBE-30) – 21 CFR 314.70(c)
  - **Moderate potential** to have an adverse effect
- Annual Report (AR) – 21 CFR 314.70(d)
  - **Minimal potential** to have an adverse effect

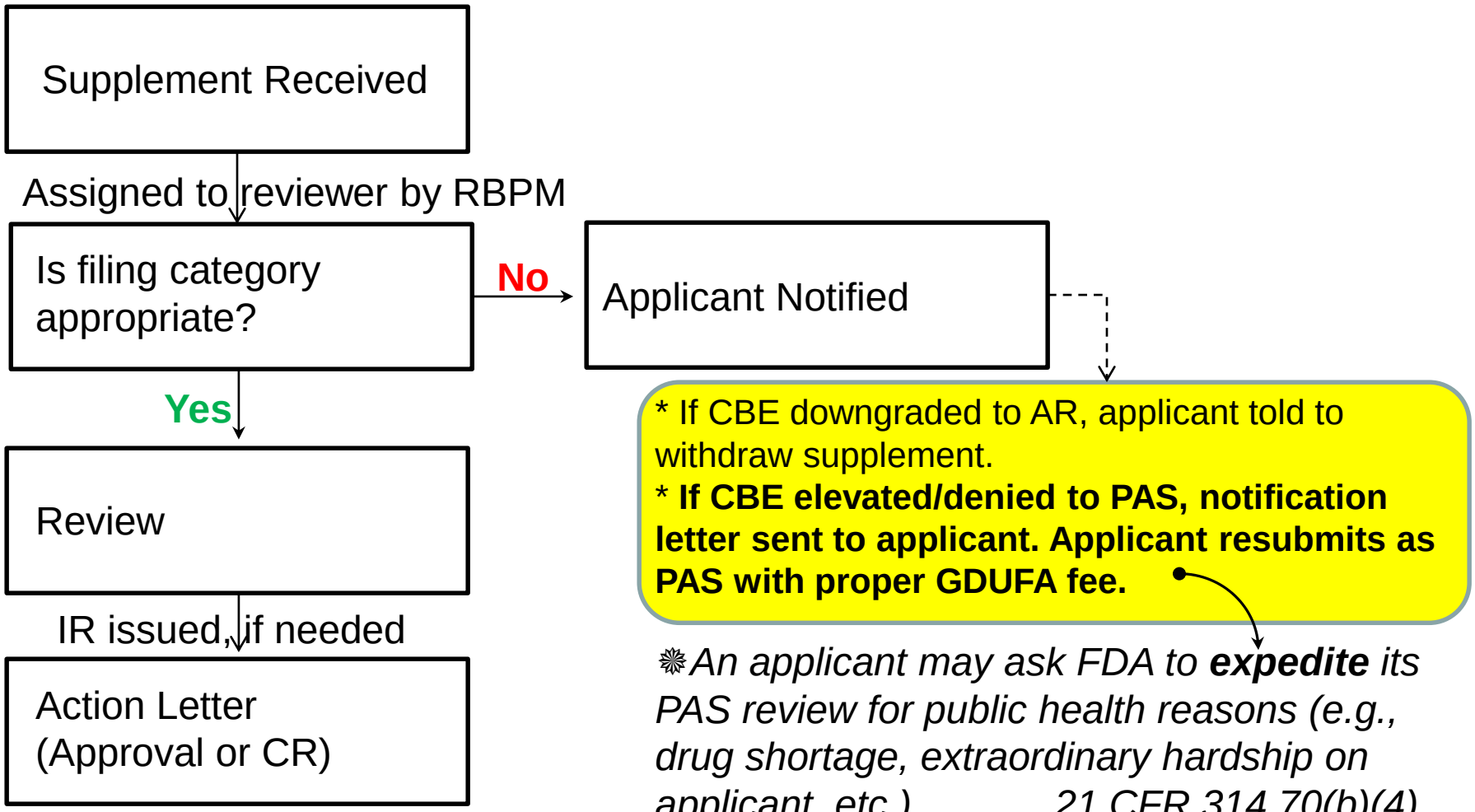
Guidances

1. Changes to an Approved NDA or ANDA (CANA, 2004)
   - Reporting categories with examples
2. SUPAC Guidances (1995, 1997)
   - Specific to dosage form type (IR, MR, and SS)
   - Change categories and supporting data
3. CMC Postapproval Manufacturing Changes to be Documented in Annual Reports (2014)
4. PAC-ATLS: Analytical Testing Laboratory Sites (1998)

Guidances & MAPPs (…contd.)

5. MAPP 5015.6: Review of Grouped Product Quality Supplements (2016)
6. MAPP 5240.3 Rev 2: Prioritization of (s)ANDA Review (revised 2016)
7. Tablet Scoring Guidance (2013)
   - Tablet splitability data to be provided for Level 2 and Level 3 changes in SUPAC
8. Comparability Protocol CMC Draft Guidance (2016)
   - CP submitted as PAS, but allows for reduced filing category for reporting the proposed change(s).

Supplement Review Process



Common Post-Approval Changes

- Manufacturing Sites
- Manufacturing Process
- Specifications (tests, acceptance criteria)
- Container Closure System
- Components and Composition
- Miscellaneous
  - Change in the approved stability protocol
  - Change in the expiration date

NOTE: If multiple related changes, most restrictive reporting category will apply.

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. Extension 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.
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 a 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)
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

Case Study 1: CBE-30 Elevated to PAS

- Proposed Change: Alternate drug product manufacturing site for an IR product
  - Supplement submitted as CBE-30 (VI.C.1.a in CANA guidance)
- Decision: Supplement was denied to PAS by FDA
- Reason: Proposed site did not have a satisfactory cGMP inspection (PAS per VI.B.2 in CANA guidance)

> A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.

Modified release (MR) solid oral dosage forms include delayed and extended release drug products.

Per SUPAC-MR, alternate drug product manufacturing site is a PAS (Level 3 change), with bioequivalence study.

Case Study 2:
CBE-30 Elevated to PAS

- Proposed Change: Delete blend uniformity analysis (BUA) testing for a **low dose drug** (0.5 mg)
  - Supplement submitted as CBE-30
- Decision: Supplement elevated to PAS by FDA
- Reason: Active drug represents 0.5 mg or only 0.6% of total tablet weight of 80 mg. Deletion of BUA is high risk. (PAS per VIII.B.2 in CANA guidance.)

Deleting any part of a specification except as otherwise provided for in this guidance (e.g., section VIII.D.2).

Common Deficiencies in Supplements

1. Comply with current USP monograph for DS and/or DP
   - E.g., ID, Assay, and Specified Impurities

2. Demonstrate method equivalency to USP

Common Deficiencies in Supplements
(…contd.)

3. DMF is Inadequate; provide revised API specification and method validation/verification

4. Provide tablet splitability data for scored tablets for Level 2/3 changes in SUPAC IR/MR
   - E.g., Change in equipment to a different design and different operating principles; alternate drug product manufacturing site, etc.

Tips to submit better supplements & avoid these common deficiencies

- Use regulations and guidances to determine the appropriate reporting category for the change and provide sufficient supporting data (e.g., per SUPAC, Tablet Scoring guidances)
  - ✓ Do not rely on data to justify classification, but instead justify reporting category based on cited guidance applicable sections and nature/risk of proposed change(s). If multiple related changes, most restrictive filing category will apply.
  - ✓ Clearly list **all** proposed changes in the cover letter.
- Keep track of USP updates
- Work with your DMF holder closely

Conclusion

- Use science-based and risk-based approach to assess product quality impact as a result of the proposed change

- Demonstrate good product and process understanding in your supplement (e.g., QbD, CQA, CPP, CMA, control strategy)

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Thank You!

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