ANDA Postapproval Changes: Best Practices and Strategies to Avoid Common Quality Assessment Issues

SBIA Generic Drugs Forum – April 2021

Niles Ron, PhD, MBA
Branch Chief (Branch 4), Division of Post Marketing Activities II
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Outline

- Risk-based classification of supplements AR, CBE, PAS
- Overview of supplement regulations, guidances, and MAPP
- Supplement review process overview
- Common post-approval changes, with generally expected reporting categories
- Case studies for incorrect supplement reporting categories
- Common deficiencies in supplements and how to avoid them
- Tips to submit better supplements, including clear cover letters

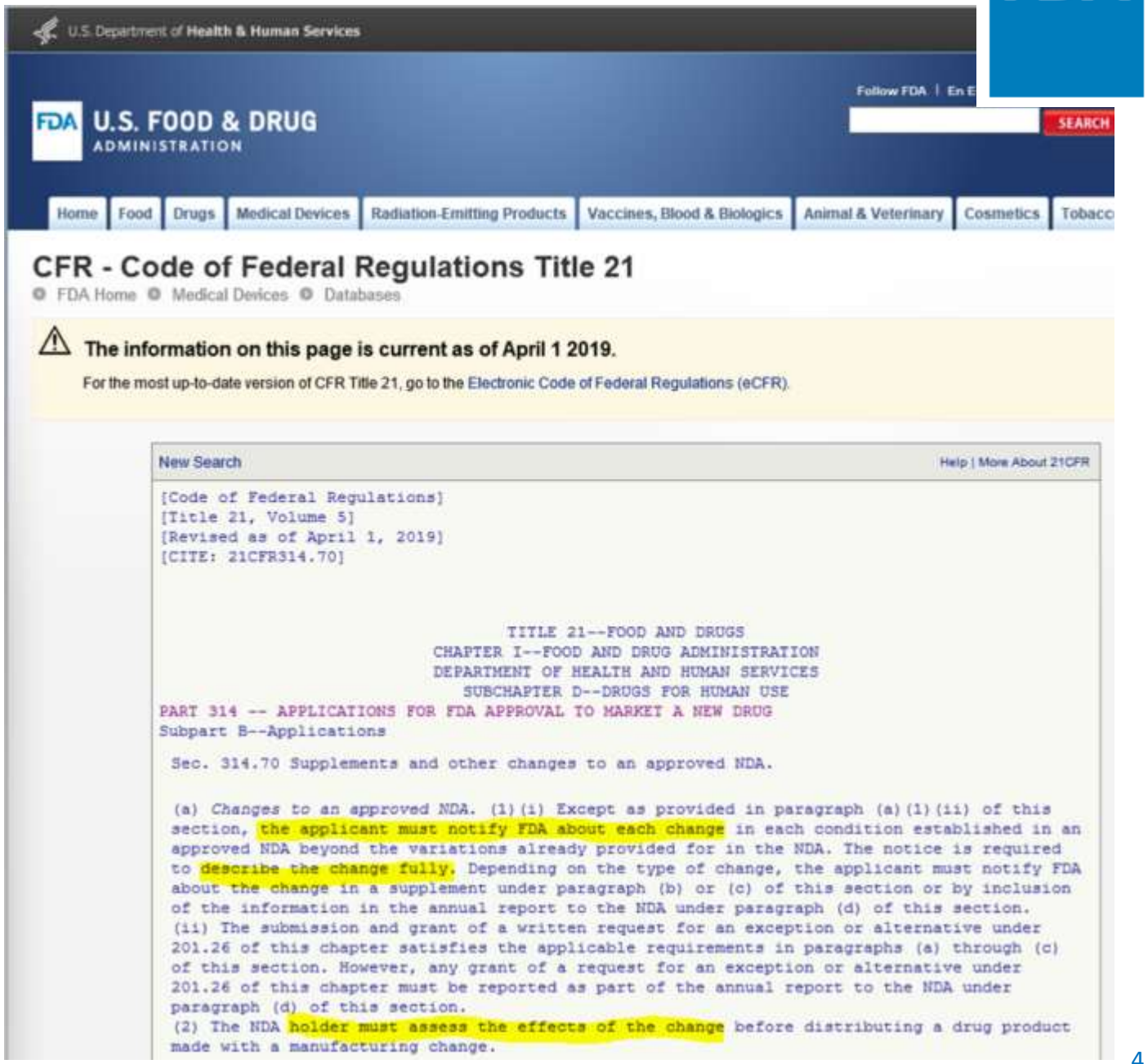
Post-Approval Change Regulation

- 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**.
- 314.70(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.
  - *i.e., provide supporting data for the proposed change(s)*

21 CFR 314.70

<u>Regulation Requirement for ANDA Sponsor:</u>

1. Submit supplement for change, if required
2. Describe change fully
3. Assess effects of the change (i.e., provide supporting data for the change)



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CFR - Code of Federal Regulations Title 21

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[Code of Federal Regulations]
[Title 21, Volume 5]
[Revised as of April 1, 2019]
[CITE: 21CFR314.70]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE
PART 314 -- APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG
Subpart B--Applications

Sec. 314.70 Supplements and other changes to an approved NDA.

(a) *Changes to an approved NDA.* (1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an approved NDA beyond the variations already provided for in the NDA. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the NDA under paragraph (d) of this section.
(ii) The submission and grant of a written request for an exception or alternative under 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under 201.26 of this chapter must be reported as part of the annual report to the NDA under paragraph (d) of this section.
(2) The NDA holder must assess the effects of the change before distributing a drug product made with a manufacturing change.

Abbreviations

- PAC = Post Approval Changes
- MAPP = Manual of Policies and Procedures
- DP = Drug Product; DS = Drug Substance; API = Active Pharmaceutical Ingredient

- PAS = Prior Approval Supplement
- CBE = Changes Being Effected
  - CBE-30: Changes Being Effected in 30 Days
  - CBE-0: Changes Being Effected in 0 Days
- AR = Annual Report

- CANA = Changes to an Approved NDA or ANDA Guidance (2004)

Risk-based Reporting Categories

Major Changes

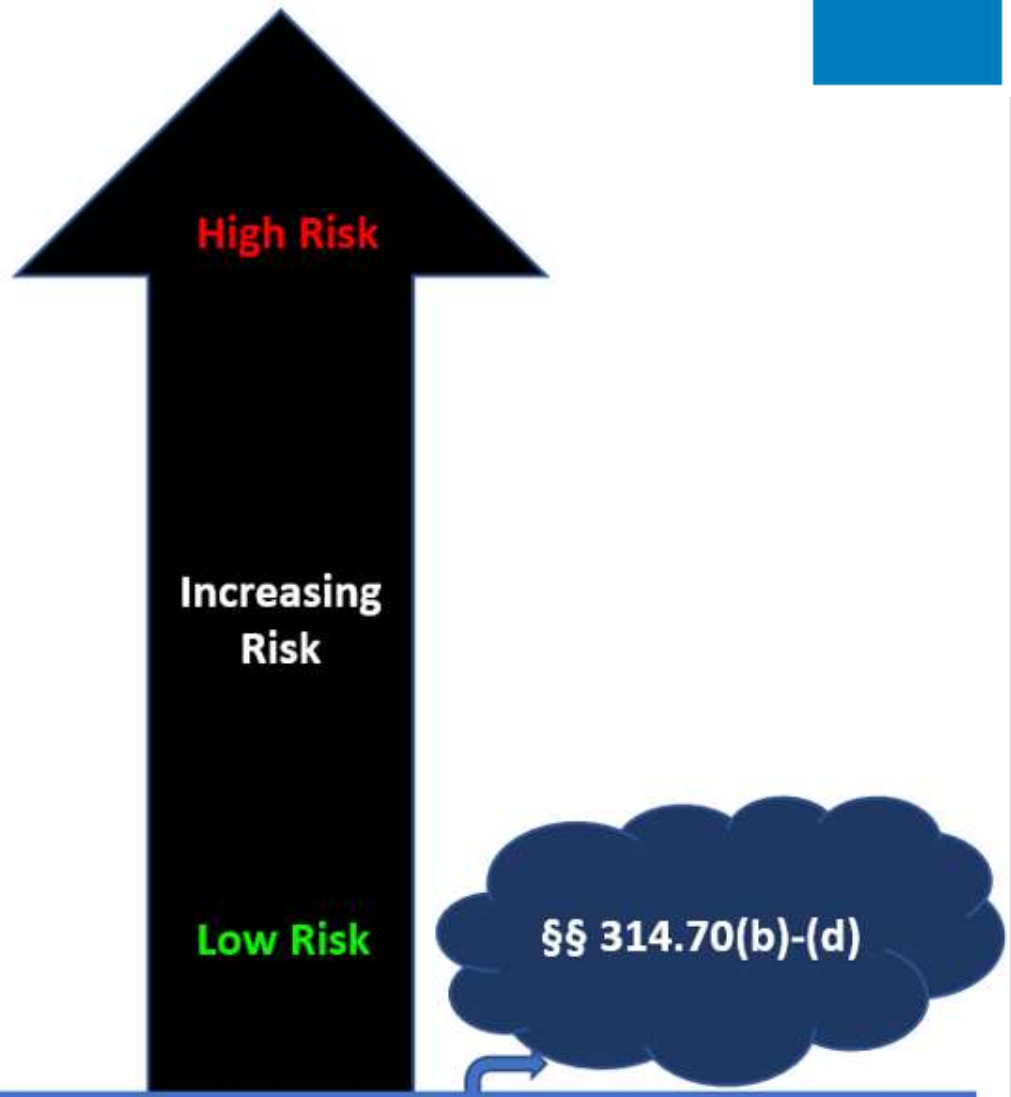
- PAS: Implement change after FDA approval

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

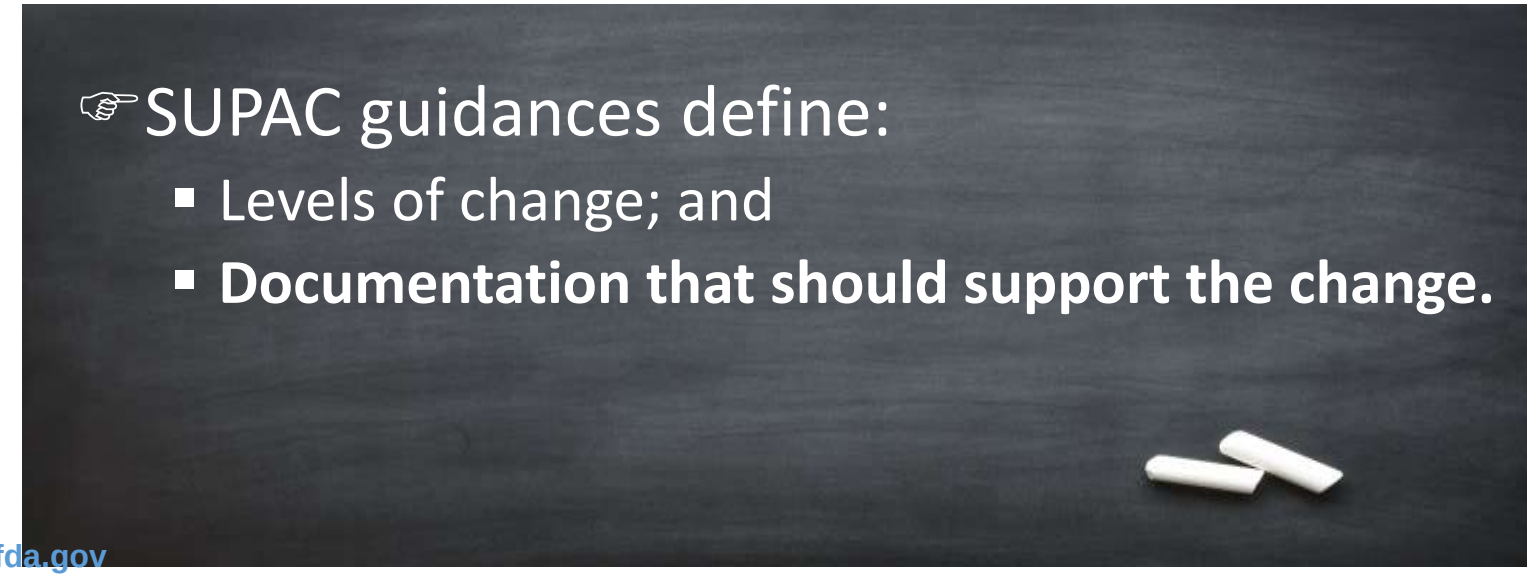


Substantial (PAS), **moderate (CBE-0/30)**, or **minimal (AR)** **potential to have an adverse effect** on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product

SUPAC: Scale-Up and PostApproval Changes

- **SUPAC-IR**: Immediate Release Solid Oral Dosage Forms (1995)
- **SUPAC-SS**: Nonsterile Semisolid Dosage Forms (1997)
- **SUPAC-MR**: Modified Release Solid Oral Dosage Forms (1997)

+ SUPAC-IR Questions & Answers (1997)
+ SUPAC: Manufacturing Equipment Addendum (2014)



Post-Market Guidances and MAPPs *(not an exhaustive listing)*

- **Changes to an Approved NDA or ANDA (GFI – April 2004)**
- Changes to an Approved NDA or ANDA Questions and Answers (GFI – Jan 2001)
- **CMC Postapproval Manufacturing Changes to be Documented in Annual Reports (GFI - March 2014)**
- **Postapproval Changes to Drug Substances (Draft GFI -Sept 2018)**
- Prioritization of the Review of Original ANDAs, Amendments, and Supplements – MAPP 5240.3 Rev. 5 (Effective Jan 2020)
- Elemental Impurities in Drug Products (GFI – Aug 2018)
- **COVID-19 Container Closure System and Component Changes: Glass Vials and Stoppers (GFI – March 2021)**

Post-Market Guidances and MAPPs *(not an exhaustive listing)*

- Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation (GFI – March 2013)

> An evaluation of the tablet splitability should be provided during the postapproval period for any product changes at Level 2 and Level 3 as defined in the Agency's Scale-up and Post-Approval Changes (SUPAC) guidances.

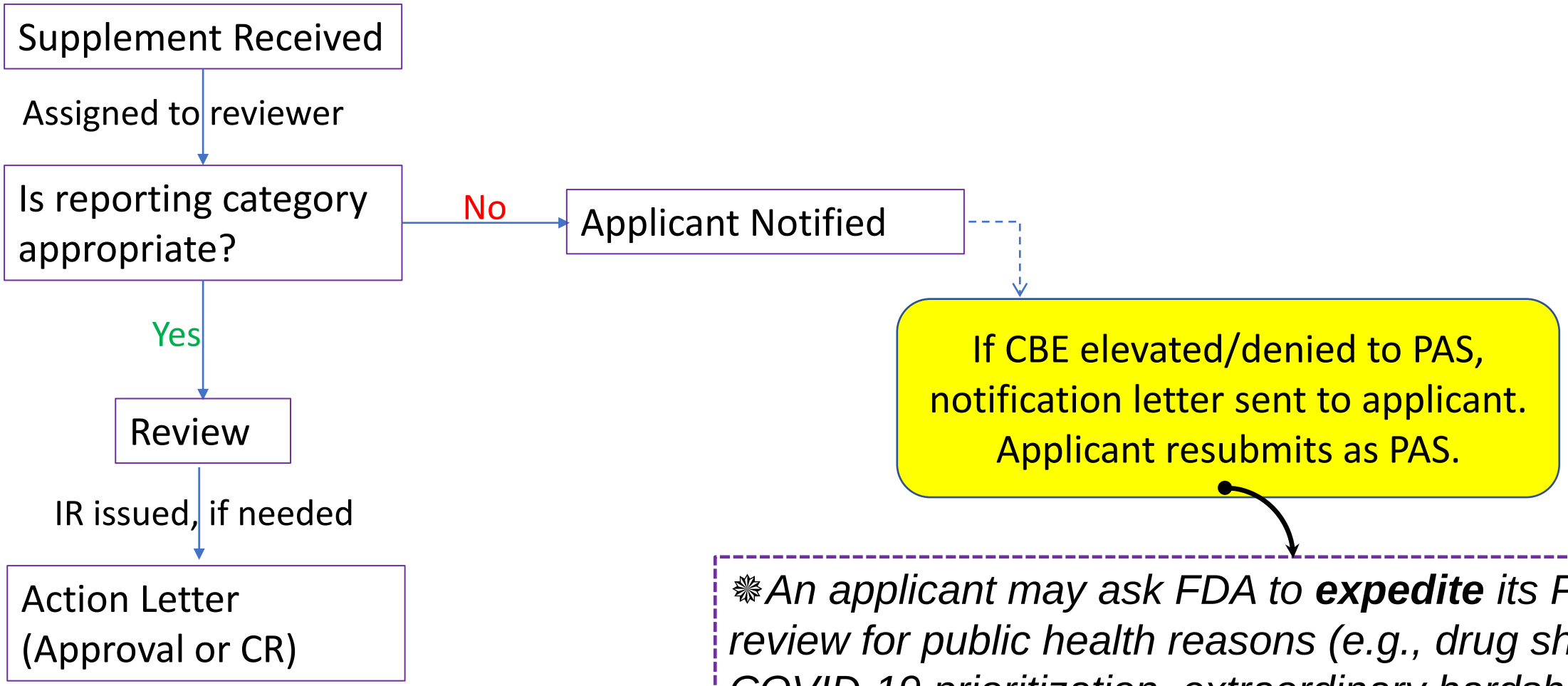
- Comparability Protocols: CMC Information (Draft GFI – April 2016)
  - CP submitted as PAS, but may allow for reduced reporting category for reporting the implementation of the proposed change(s).

Post-Market Guidances and MAPPs *(not an exhaustive listing)*

- PAC-ATLS: Analytical Testing Laboratory Sites (1998)
- **MAPP 5015.6: Review of Grouped Product Quality Supplements (2016)**
  - Cover letter should clearly state the purpose of the proposed CMC changes and indicate that the supplement is one of multiple submissions for the same change

Supplements cannot be grouped if submitted by a different applicant or if the supplements provide for different CMC changes. The supporting data necessary for the review of the CMC changes should be the same for each of the grouped supplements. Any supplement that provides for the same CMC changes but necessitates the review of data that is unique to that supplement (e.g., product-specific data) should not be grouped.

Supplement Review Process



❁*An applicant may ask FDA to **expedite** its PAS review for public health reasons (e.g., drug shortage, COVID-19 prioritization, extraordinary hardship on applicant, etc.)* *21 CFR 314.70(b)(4) & MAPP 5240.3*

Common Post-Approval Changes

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

NOTE: If a supplement provides for multiple related changes, the **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.
7. For DPs that do not exceed the Permitted Daily Exposure (PDEs), changes made to elemental impurity controls to comply with USP <232>/ICH Q3D.

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 (e.g., widening impurity limits to accommodate failing data) or deleting tests (e.g., in-process blend uniformity analysis)
4. Equipment of different operating principles (e.g., oven tray dryer vs. fluid bed dryer for drug product)
5. Introducing a blister pack (when currently approved packaging is bottles)
6. Add new flavor or color
7. Drug product manufacturing site change for a modified release product
8. Adding a new strength

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 both 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 denied 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).

Case Study 3: CBE-30 Elevated to PAS

- Proposed Change: Alternate/new API source
  - Supplement submitted as CBE-30
- Decision: Supplement denied to PAS by FDA
- Reason: Alternate source of the API should be a PAS as per Guidance for Industry – Changes to an Approved NDA or ANDA Questions and Answers (January 2001), Manufacturing Sites – Q1/A1 and Draft Guidance for Industry – Post approval Changes to Drug Substances (September 2018), Section XI.
  - Typically, such a change involves more than simply a site change. In most cases, there will be additional differences (e.g., route of synthesis, process, solvents, equipment).
  - A change to a new source of the drug substance is considered to have a high *potential* to have an adverse effect on the drug substance's impurity profile and physical properties.

Case Study 3: Alternate API Source (…contd.)

- ***Once the proposed alternate API source supplement is approved as a PAS for the same applicant***, and if there are no other changes to be reported that would otherwise belong in a PAS-type reporting category, ***the applicant can report the same change (i.e., the same alternate API source) for their other drug products as a CBE-30***, provided the API manufacturing/testing site(s) has a satisfactory cGMP inspection status.
  - **The applicant should identify in the subsequent CBE-30 supplement for the alternate API source, the approved PAS for the same change for the same applicant.**

Common Deficiencies in Supplements & How to Avoid them

1. Comply with current USP monograph for DS and/or DP
   - E.g., ID, Assay, and Specified Impurities
     - ☑ Keep track of USP updates for new or revised monographs

2. Demonstrate method equivalency to USP
   - ☑ For in-house methods, validate method and demonstrate same or increased assurance of quality as the analytical procedure described in the USP

Common Deficiencies in Supplements (…contd.)

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

   ☑ Work with the DMF holder closely to resolve issues promptly

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 DP manufacturing site; formulation change, etc.

     ☑ Check the guidance [Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation (2013)] upfront for split tablet data requirements to support score for Level 2/3 changes to drug product

Tips to Submit Better Supplements

- Use regulation and guidances to determine the appropriate reporting category for the change and provide sufficient supporting data (e.g., per SUPAC, tablet scoring, PAC drug substances guidance)
  - Do not rely on data to justify supplement classification, but instead justify reporting category based on cited guidance applicable sections and nature of proposed change(s).
- Clearly list **all** proposed changes in the cover letter, along with a discussion and summary of the provided supporting data.
- Cross-reference other pending or approved supplements with the same/similar proposed change(s).
- For PAS re-submission based on CBE denied to PAS, reference the FDA communication.

Tips to Submit Better Supplements

- DMF-Related Changes: Clearly state in the cover letter the DMF number and date of the specific DMF amendment that incorporates the proposed change.
  - **Supporting Data**:
    - Refer to Postapproval Changes to Drug Substances Draft Guidance (September 2018) for supporting data needed.
    - Generally, submission should minimally include Certificate of Analysis (COA) for the post-change API from both the drug substance and drug product manufacturer.

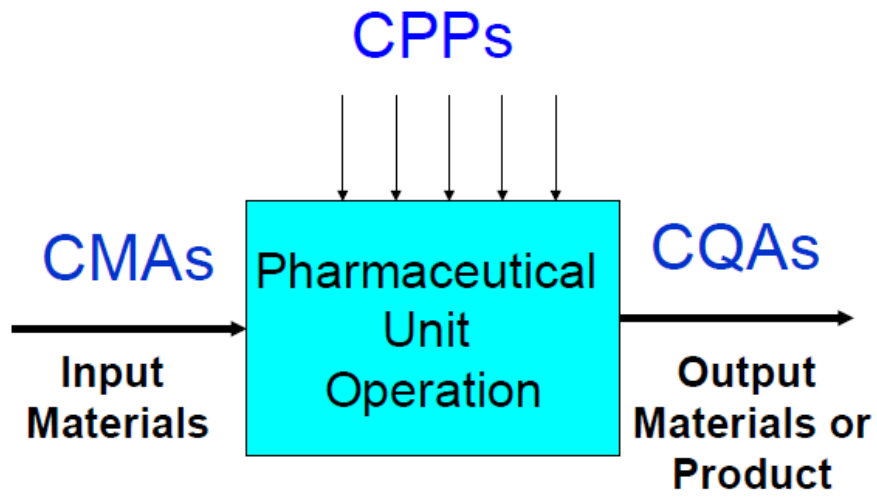
Example of List of Changes in Cover Letter

#	Change Description	Filing Category	Justification for Change Classification by Guidance and Risk Basis
1	Changes in drug substance manufacturing process, as per DMF # 12345 amendment dated September 10, 2020	CBE-30	Per Guidance for Industry: Changes to An Approved NDA or ANDA, April 2004, VII.C.1.b "For drug substances, any change in process and/or process parameters except otherwise provided for in this guidance" may be submitted in a CBE-30 supplement. Therefore this change is being submitted as a CBE-30.
2	Change in specifications to align drug substance Assay and Related Substances with USP	CBE-30	Per Guidance for Industry: Changes to An Approved NDA or ANDA, April 2004, VIII.C.1.e, "Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements."
3	Modification of Drug Product specifications to include "Meets ICH Q3D requirements. No Testing Required" for Elemental Impurities	AR	Supporting an annual reportable filing is Elemental Impurities in Drug Products, Guidance for Industry, August 2018, Section III.E: "Such changes made to comply with General Chapters <232> and <233> are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product and must be documented by the applicant in the next annual report in accordance with 21 CFR 314.81(b)(2)."
4	Change in analytical method for residual solvents in drug product	CBE-30	Guidance for Industry – Changes to an Approved NDA or ANDA (April 2004), Section VIII.C.1.a, "Any change in a regulatory analytical procedure other than those identified as major changes or editorial changes."

Conclusion

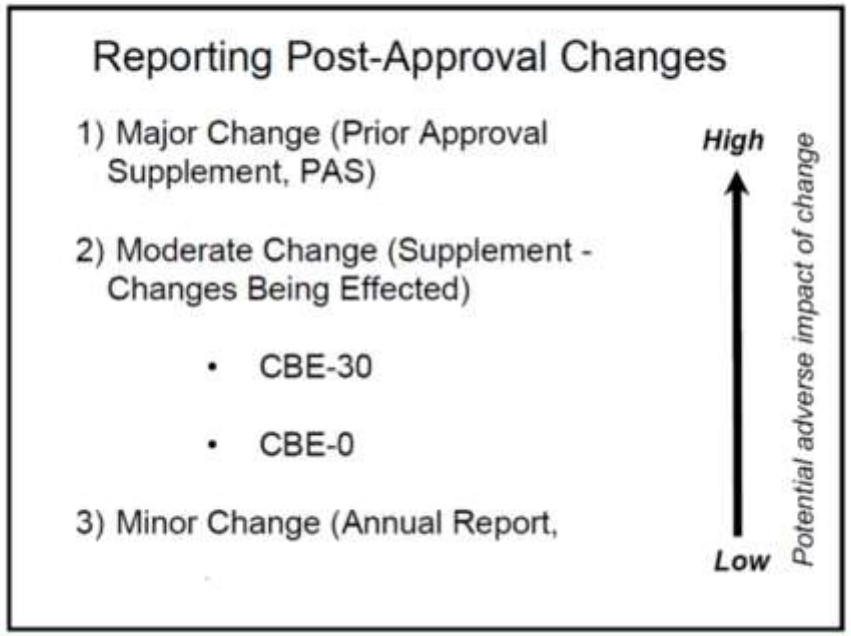
- Use **science-based and risk-based approach, plus guidance & supporting data**, to assess product quality impact as a result of the proposed change(s)
- Demonstrate good product and process understanding in your supplement (e.g., QbD, CQA, CPP, CMA, control strategy)

Relationship between CMAs, CPPs and CQAs



$$CQAs = f(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

Risk-Based PAC Reporting Categories

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Challenge Questions

1. Which regulation is for supplements and other changes to an approved application?

   - ❑ **21 CFR 314.70**
   - ❑ 12 CFR 1006.1

2. Deletion of blend uniformity testing for a low dose drug belongs to which reporting category?

   - ❑ CBE-30
   - ❑ **PAS**