Common Quality Deficiencies in Supplemental ANDAs

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Disclaimer

This talk reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- ANDA Supplement Regulations and Risk-Based Classification
- Common ANDA Post-Approval Quality Changes
- Common Deficiencies in ANDA Supplements (sANDA) and How to Avoid Them
- Best Practices for Submitting Better Supplements

Post-Approval Change Regulation Requirements for ANDA Sponsors

- 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.

CFR - Code of Federal Regulations Title 21 (fda.gov)

Risk-based Reporting Categories

Major Changes (High risk)	Moderate Changes (Moderate risk)	Minor Changes (Low risk)
• Prior Approval Supplement (PAS) • Implement change after FDA approval	• Changes Being Effected in 0 Days (CBE-0): Implement change immediately after supplement receipt at FDA • CBE-30: Implement change 30 days following supplement receipt at FDA	• Annual report (AR) • Implement immediately

Changes with **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

Helpful Guidances Documents (non-exhaustive)

- **Changes to an Approved NDA or ANDA, 2004**
  - **Q&A, 2001**
- CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports, 2014
- Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation
  - **SUPAC IR, 1995**
  - **SUPAC IR Q&A, 1997**
  - **SUPAC MR, 1997**
  - **SUPAC SS, 1997**
  - **SUPAC: Manufacturing Equipment Addendum, 2014**
- **PAC-ATLS: Postapproval Changes —Analytical Testing Laboratory Sites, 1998**
- **Postapproval Changes to Drug Substances, 2018 (Draft)**
- Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation, 2013
- **Microbiological Quality Considerations in Non-sterile Drug Manufacturing, 2021**
- **MAPP 5016.6 - Change in Hard Gelatin Capsule Shell Supplier**
- **Control of Nitrosamine Impurities in Human Drugs, 2024**
- **Replacing Color Additives in Approved or Marketed Drug Products 2025 (Draft)**

Guidances/MAPP in bold include recommended reporting categories

Common ANDA Post-Approval Quality Changes

Drug Substance:	New source, manufacturing process, specifications, analytical procedures
Drug Product:	Formulations (new strengths, excipients), manufacturing process, equipment, batch sizes, in-process controls, specifications, analytical procedures, container closure, stability protocol, shelf life
Facilities:	Manufacturing, testing, and packaging sites

Two-Step Supplement Review Process

- **Step I:** Risk assessment of proposed changes to determine proper reporting category
- **Step II:** In-depth review of changes with supporting data/information leading to approval or deficiency determination

Common Drug Substance Deficiencies in sANDA

- **Inadequate DMF** – Deficiency identified in the referenced DMF for drug substance. DMF holder is notified about the deficiencies
  - ✓ Maintain close communication with the DMF holder to resolve issues promptly

- **Incomplete Facilities Information** – Missing details (name, address, FEI#, responsibility) for contractors involved in manufacturing and release testing referenced in DMF
  - ✓ Ensure all facilities referenced in DMF are submitted for assessment and properly documented

Common Drug Substance Deficiencies in sANDA

- **Missing CoAs** – Submission lacks Certificates of Analysis from both supplier and drug product manufacturer for drug substance manufactured with proposed changes

- **Inadequate Method Validation** – Insufficient or missing analytical method validation/verification data to demonstrate that test methods are suitable for their intended use

  ✓ Use regulations and guidances to determine appropriate supporting data requirements

Common Drug Product Deficiencies in sANDA

- **Facility** – Manufacturing site does not have satisfactory cGMP inspection
  - ✓ Verify Facility Compliance

- **USP Non-Compliance** – Drug product does not comply with current USP monograph requirements
  - ✓ Track USP updates regularly for new or revised monographs to ensure ongoing compliance

Common Drug Product Deficiencies in sANDA

- **Missing Method Equivalency** – Failure to provide USP method equivalency documentation

- **Missing Splitability Data** – Missing tablet splitability data for scored tablets in Level 2/3 SUPAC IR/MR changes

✓ Apply regulatory guidance (e.g., SUPAC, tablet scoring guidance, nitrosamine guidance) to determine supporting data requirements

Best Practices for Submitting Better Supplements

- Include **all** changes in the cover letter with an itemized list of changes.
- Include reporting category for each change and provide justification based on regulations and guidance, not data. For multiple changes, provide a summary table listing each change and its classification with justification for each.
- If there is supporting Pharm/Tox information, then state it in the cover letter and reference where the information can be found in the supplement.
- Follow current FDA guidance (e.g., CANA, SUPAC, tablet scoring guidance, nitrosamine guidance) to determine appropriate reporting category and supporting data requirements.


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Common Reasons for CBE 0/30 Denials to PAS

Drug substance	• Changes in the drug substance synthesis that may affect its impurity profile and/or the physical properties
Components	• Change in the technical grade of an excipient
Site change	• Drug product manufacturing site change when the site has never been inspected for the type of operation being proposed or does not have a satisfactory cGMP inspection • Drug product manufacturing site change for a modified release product

Common Reasons for CBE 0/30 Denials to PAS

In-Process	• Deletion of CQA from in-process controls for commercial batches (e.g., Blend uniformity for low dose product)
Drug product	• Deletion of microbiological testing from the release and/or stability for non-sterile solid dosage forms
Container Closure	• Additional Packaging configuration (e.g., Blister pack or Unit dose cup)
Stability	• Reduction in the stability testing time points (e.g., “Initial, 3, 6, 9, 12, 18, and 24 month” to “Initial, 6, 12, and 24 month”)