



Understanding Regulatory Expectations for Post-Approval Changes in ANDAs

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Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Drugs are no different.

A close-up photograph showing a hand holding an orange pill bottle and pouring three white, oval-shaped pills into the palm of another hand. The background is softly blurred, focusing attention on the action of taking medication.

**Patients expect safe and effective
medicine with every dose they take.**

A close-up photograph of a person's hand holding an orange pill bottle, pouring three white, oval-shaped pills into their palm. The background is softly blurred, showing the person's face and another hand. The text is overlaid on the image in a white, sans-serif font.

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

A close-up photograph of a person's hands. The left hand holds an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the right hand. The background is softly blurred, showing a person's face in profile.

**It is what gives patients confidence
in their *next* dose of medicine.**

Communication Expectations and Best Practices



OUTLINE



- Form FDA 356h
- Supplement Cover Letter
- Module 3
- Drug Master File facility related changes
- Drug Substance Manufacturing Process Changes
- Facility related changes
- Nitrosamine Risk Assessment Reports
- Submission Status Inquiries
- Grouped Supplements
- Priority Review Requests
- Secure Email
- Post Marketing Inquiries

FORM FDA 356h



- Use Updated version (08/18) - <https://www.fda.gov/media/72649/download>
- Address status (i.e. pending, active, inactive, and withdrawn) for all facilities within your application and not limited to the submission
- Update with subsequent submissions
- Include all relevant manufacturing facilities associated with the application. See FDA Guidance for Industry: [Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers](#) for information on which facilities need to be included on Form 356h and other sections of the supplemental application
- All Manufacturing/Packaging/Testing sites used by the referenced Drug Master File (DMF)

FORM FDA 356h



- Drug Substance Manufacturing Facilities including the following;
 - Critical Intermediate manufacturing facilities
 - Routine/Skip Testing facility used for release and stability specifications
 - Micronization Facilities
 - Sterilization Facilities
- Field 24 – Indicate if the product proposed within the submission is a combination product [e.g., drug-device, drug-biological product, drug-device-biological product, see 21 CFR 3.2(e)]. <https://www.fda.gov/combination-products/about-combination-products>

SUPPLEMENT COVER LETTER



- Clearly identify the overall proposed change classification as either CBE-0, CBE-30, or PAS. For multiple changes, a summary table listing each changes and the classification with justification for each

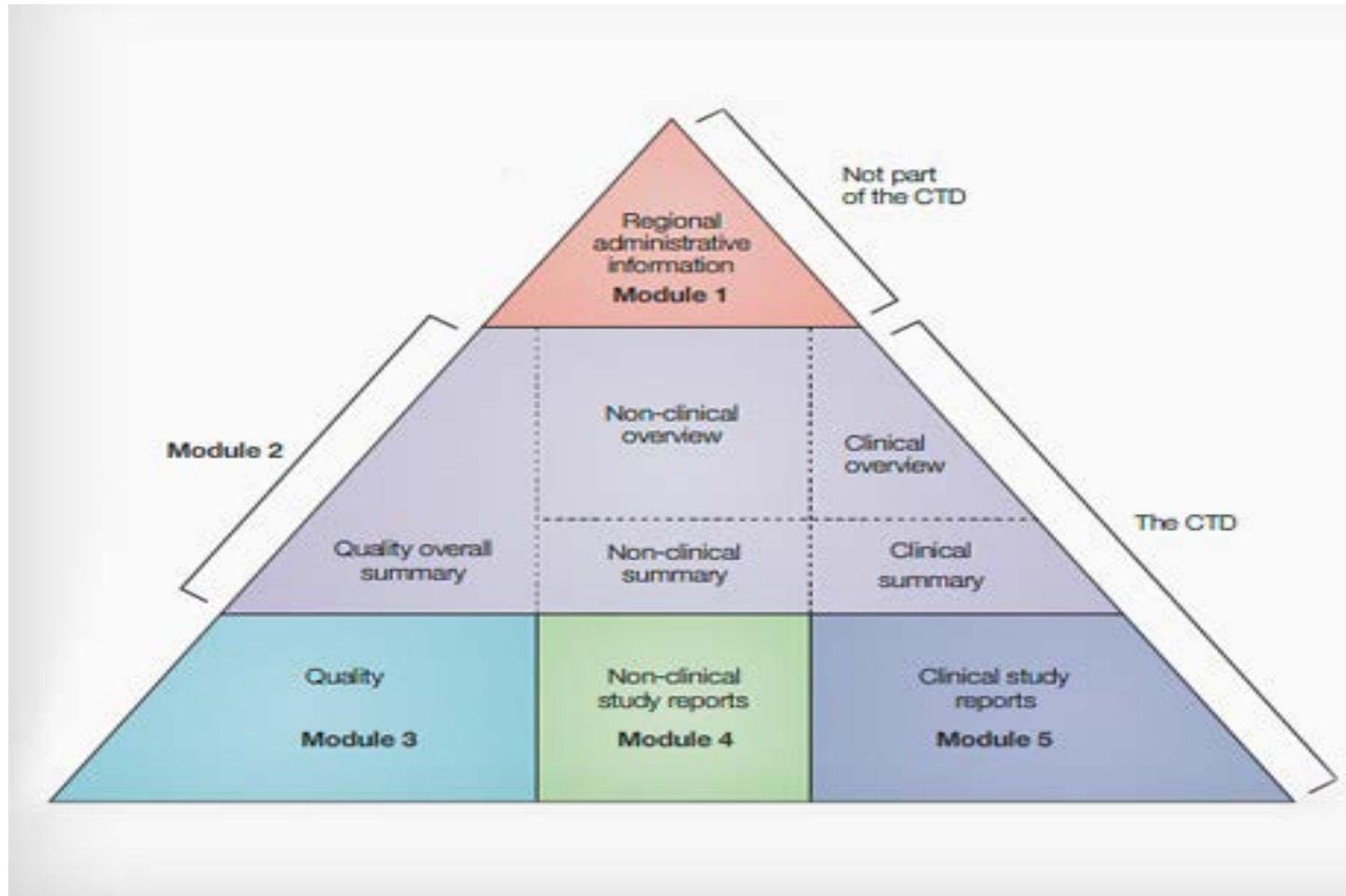
Change Description	Filing Category	Basis for Classification
Removal of excipient Identification Test C testing to align with USP	CBE-30	<p>Guidance for Industry, Changes to an Approved NDA or ANDA, April 2004, Section VIII.C.1.e, classifies “Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements” as a CBE-30 supplement.</p> <p>As such, the change to delete the excipient Identification Test C testing to align with the USP monograph aligns with the CBE-30 filing category.</p>
Removal of excipient heavy metal specification to align with USP	Annual Report	<p>FDA Guidance for Industry, Changes to an Approved NDA or ANDA, 2004, Section VIII.C.1.e, classifies “Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements as a CBE-30 supplement.</p> <p>However, per Guidance for Industry: Elemental Impurities in Drug Products, Guidance for Industry, June 2016, Section III.E: changes made to comply with General Chapters <232> and <233> which follow the recommendations of ICH Q3D are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product may be reported in an annual report.</p> <p>The excipient supplier performed a Risk Assessment in alignment with ICH Q3D guidance. The assessment concluded that the elemental impurity levels are consistently below 30% of the control threshold so additional controls are not required.</p>

SUPPLEMENT COVER LETTER



- All proposed changes in the entire submission (including all facility changes which will be noted in module 3)
- Any referenced Drug Master File (DMF)? Include the DMF #
- Is submission based on a specific DMF amendment? Reference the DMF amendment letter to the agency or submission date in the cover letter
- Are there other previously pending, recent, or approved submissions with the same/similar proposed change(s)? Include the information
- For PAS submission based on CBE denied to PAS reference the FDA communication

MODULE 3



MODULE 3



- Section of the common technical document (CTD) regulatory submissions format that contains all the required quality information and data corresponding to the registration of a pharmaceutical product. Includes requirements for presenting manufacturing, characterization, drug substance controls, stability characteristics, descriptions and compositions of pharmaceuticals, and other essential information.
- All intended CMC changes should be accompanied with information in this module and not only limited to description of changes in the cover letter
- If an excipient is considered critical to the drug product performance, the testing facilities should be listed under this module

Drug Master File Facility Related Changes



- Agency will consider all facilities that are listed in a DMF apply to the referencing ANDA application(s) unless explicitly stated in the DMF Letter of Authorization (LOA) that only certain facilities will be used by the referencing application
- Addition of critical DMF intermediates and testing sites which impact your application requires submission of a supplement
- Prior to submitting supplement for DMF related changes such an alternate API source, etc. communicate with DMF holder to inquire about status of their DMF to avoid delays or unexpected outcomes especially prior to submitting Complete Response deficiencies. This also includes cGMP status of their manufacturing sites.

DRUG SUBSTANCE MANUFACTURING PROCESS CHANGES



- Submissions should include Certificate of Analysis (CoA) for both the Drug Substance and Drug Product Manufacturer
- If either is missing an Information Request will be issued and this may potentially delay filing classification

Facility Related Changes

- Awareness of most recent cGMP surveillance classification for the proposed facility from business partners
- Resource: FDA Inspection Database: <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database>
 - Not all inspections are included in the database. Inspections conducted by States, pre-approval inspections, mammography facility inspections, inspections waiting for a final enforcement action, and inspections of nonclinical labs are not included. Inspections of nonclinical labs are available at [Nonclinical Laboratories Inspected under Good Laboratory Practices](#).
 - The results show final classifications of [No Action Indicated \(NAI\)](#), [Voluntary Action Indicated \(VAI\)](#), [Official Action Indicated \(OAI\)](#) for each [project area](#) within an inspection.

NITROSAMINE RISK ASSESSMENT REPORTS



- The risk assessment reports, and any risk determined therein, are generally not assessed in application evaluation
- In accordance with the Guidance for Industry Control of Nitrosamine Impurities in Human Drugs (final, February 2021), risk assessment reports should not be submitted to the Agency for review but should be retained so that these documents are available upon request from a manufacturing site.
- However, where nitrosamines are detected, changes implemented to prevent or reduce nitrosamine impurities in active pharmaceutical ingredients and drug products should be reported in accordance with 21 CFR 314.420(c) and changes to approved applications as required under 21 CFR 314.70 and 314.97 and pending applications under 21 CFR 314.60 and 314.96



Submission Status Inquiries

- All CBE grant determinations, 30 days from the FDA receipt date
- Completion of CBE assessments, generally 6-10 months from FDA receipt date (except for drug shortage or Public Health Emergency situations)
- Prior Approval Supplements, Acknowledgement Letter issued generally no later than day 30 from FDA receipt date

TIMELINES (PAS)

Submission Type	General Expected Completion
Standard PAS or PAS Major Amendments	6-10 months depending on preapproval inspection requirements
Priority PAS or PAS Major Amendments	4-10 months depending on preapproval inspection requirements, submission of complete and accurate Pre-Submission Facility Correspondence (PFC)
Standard and Priority PAS Minor Amendments	3 months



Grouped Supplements



- Refer to [MAPP 5015.6 Rev 1](#) – Office of Pharmaceutical Quality Review of Grouped Product Quality Supplements
- Identical CMC post-approval changes that affect multiple approved applications
- Two or more supplements reviewed and processed using the procedures and assigned to same assessment team
- **The supporting data necessary for the review of the CMC changes should be the same for each of the grouped supplements**

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 – However, should be mentioned in the cover letter
- The cover letter for the supplements should clearly state the purpose of the proposed CMC changes and indicate that the supplement is one of multiple submissions for the same change
- Submit cover letter and module 3 information to each supplement within the group

PRIORITY REVIEW REQUESTS



- [MAPP 5240.3 Rev. 5](#) – Office of Generic Drugs Prioritization of the Review of Original ANDAs, Amendments, and Supplements
- FDA will only consider a request for priority review when (1) the cover letter to the submission clearly states “Priority Review Requested” and references the ANDA number; (2) the basis for the request is consistent with this MAPP; (3) the applicant clearly and briefly states the basis for the request, including the prioritization factor(s); and (4) the **applicant includes sufficient supporting documentation for the request**
- If a Complete Response Letter is issued, the resubmission needs to follow the same process if you desire a priority review

SECURE EMAIL



- FDA communications via unsecure email cannot include commercial confidential information (e.g. application numbers or information, trade secrets, manufacturing, or patient information). Therefore, sponsors/applicants should establish secure email with FDA to allow for informal communications that may include commercial confidential information
- This applies to all applicants and DMF holders
- Unsecure email leads to communication delays
- If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov

POST-MARKETING INQUIRIES



- Manufacturing (CMC) Supplements: Contact the Project Owner OGD RPM or OPQ RBPM who issued the Acknowledgement Letter
- Controlled Correspondence: Inquiries concerning CMC post-approval submission requirements that are not covered by CDER post-approval changes guidance and are not specific to an abbreviated new drug application (ANDA) should be submitted via a Standard Controlled Correspondence using the [CDER Direct NextGen Collaboration Portal](#)
- Inquiries about CMC post-approval submission requirements which do not qualify as controlled correspondence and not covered under any of the CDER post-approval guidances: CDER-OPQ-Inquiries@fda.hhs.gov



POST-MARKETING INQUIRIES

- Labeling Supplements: - genericdrugs@fda.hhs.gov
- ANDA Transfer of Ownership, Withdrawal and Consolidation are managed by the Office of Generic Drugs - genericdrugs@fda.hhs.gov



Thank you!

