



CMC Considerations for 505(b)(2) Applications

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Outline

- Introduction
- Brief overview of FDA drug approval pathways and 505(b)(2) regulatory considerations
- CMC considerations for 505(b)(2) and drug combination products
- Summary

Approval Pathways Under the Federal Food, Drug, and Cosmetic Act (FFD&C Act)

- New Drug Applications (NDAs)
 - Stand-alone NDA (505(b)(1) application)
 - 505(b)(2) application
- Abbreviated New Drug Applications (ANDAs)
 - “Duplicate” of a listed drug (same active ingredient, dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics); or
 - Drug product that differs from the listed drug in specified ways and for which FDA has approved a “suitability petition” based on its determination that approval would be warranted without additional clinical safety and effectiveness (S&E) data (see FFD&C Act §505(j)(2)(C))

The 505(b)(2) Approval Pathway

- 505(b)(2) applications contain full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.
- A 505(b)(2) applicant may rely upon:
 - FDA’s finding of safety and/or effectiveness for one or more listed drugs (includes approved product labeling, product-specific published literature)
 - OTC monograph establishing conditions under which the drug is GRAS/E
 - Published literature (includes non-product-specific published literature, literature submitted to DESI docket)

Other 505(b)(2) Regulatory Considerations

- The applicant may rely on FDA’s finding of S&E for one or more listed drug(s) only to extent that proposed product shares characteristics in common with the listed drug(s):
 - Establishing that reliance is scientifically justified
 - Establishing a “bridge” (e.g., via comparative bioavailability (BA) data) between the proposed drug product and each listed drug relied upon
- The applicant may rely on published literature or other studies if applicant establishes that such reliance is scientifically justified.
- To the extent that the listed drug(s) and the proposed drug product differ, the 505(b)(2) application must include sufficient data to demonstrate that the proposed drug product meets the statutory approval standard for safety and effectiveness (see 21 CFR 314.54(a)).

Other 505(b)(2) Regulatory Considerations

- FDA may refuse to file a 505(b)(2) application for a drug that is a “duplicate” of a listed drug and eligible for approval under 505(j).
 - A “duplicate” of an approved combination product generally means a drug product with the same combination of active ingredients, dosage form, route of administration, strength, labeling, and conditions of use, not just the same individual components as previously approved.

CMC Information Required in a 505(b)(2) NDA

- 21 CFR 314.50(d)(1) – The application is required to contain a full description of the chemistry, manufacturing, and controls (CMC) information.
 - Drug Substance: Physical and chemical characteristics, manufacturer, method of synthesis and purification, process controls, specifications, and stability
 - Drug Product: Components, composition, specifications for each component, manufacturer, description of manufacturing and packaging procedures, in-process controls, specifications, and stability
- 21 CFR 314.54 – Procedures for submission of an application requiring investigations for approval of a new indication for, or other change from, a listed drug
 - Refers to information required under 314.50 that must be submitted for 505(b)(2) applications (these include full CMC)

Drug Master Files (DMFs)

- Not all of the CMC information relevant to a drug product is always submitted by the applicant to the NDA; sometimes some of the information is referenced to a DMF
 - DMFs are reviewed only if a Letter of Authorization (LOA) is provided by the DMF holder
 - DMFs are reviewed only for the referenced information to support the application
 - The location(s) of the supportive information in the DMF should be provided
 - The information is confidential; not revealed to the NDA applicant

Organization of NDA

- NDA submissions are organized in accordance with the “Common Technical Document” (CTD) format
 - Established by International Conference on Harmonization (ICH)
 - Refer to ICH guidances
- Key sections of document
 - Module 1: Mostly administrative information (region specific)
 - Module 2: Summaries of the information provided (in full) in the remaining modules
 - Includes a quality-related subsection called the Quality Overall Summary (QOS) – provides high level overview of critical information
 - Module 3: Quality
 - Drug Substance(s)
 - Drug Product (including excipients and packaging components)
 - Module 4: Preclinical
 - Module 5: Clinical

Module 3

3.2.S Drug Substance

- S.1 General Information
 - Nomenclature
 - Chemical structure
 - General properties of the drug substance
- S.2 Manufacture
 - Manufacturers (including analytical testing facilities)
 - Description of manufacturing process and process controls
 - Control of materials
 - Controls of critical steps and intermediates
 - Process validation and/or evaluation
 - Manufacturing process development

Module 3

3.2.S Drug Substance

- S.3 Characterization
 - Elucidation of structure
 - **Are physical properties important?**
 - Impurities
 - **Any new impurities? Are they qualified?**
- S.4 Control of Drug Substance
 - Specification
 - Analytical procedures
 - Validation of analytical procedures
 - Batch analyses
 - Justification of specification

Module 3

3.2.S Drug Substance

- S.5 Reference Standards or Materials
- S.6 Container Closure System
- S.7 Stability
 - Stability summary and conclusions
 - Post-approval stability protocol and stability commitment
 - Stability data

Module 3

3.2.P Drug Product

- P.1 Description and Composition
- P.2 Pharmaceutical Development
 - Components of the drug product
 - Drug substance
 - **Drug-drug compatibility for combination products**
 - » Compatible Actives – can mix active ingredients into one formulation, if desired
 - » Non-compatible Actives – may need to keep active ingredients physically separated to minimize reactions, e.g., bilayer tablets
 - **Compatibility of active ingredient(s) with excipients**
 - Excipients

Module 3

3.2.P Drug Product

- P.2 Pharmaceutical Development (continued)
 - Drug product
 - Formulation development
 - **Rationale for new formulation for combination product?**
 - Overages
 - Physicochemical and biological properties
 - Manufacturing process development
 - Container closure system
 - Microbiological Attributes
 - Compatibility

Module 3

3.2.P Drug Product

- P.3 Manufacture
 - Manufacturers (including testing and packaging facilities)
 - Batch formula
 - Description of manufacturing process and process controls
 - Controls of critical steps and intermediates
 - Process validation and/or evaluation
- P.4 Control of Excipients
 - Specifications
 - Analytical procedures
 - Validation of analytical procedures
 - Justification of specifications
 - Excipients of human or animal origin
 - Novel excipients

Module 3

3.2.P Drug Product

- P.5 Control of Drug Product
 - Specification(s)
 - Analytical procedures
 - Validation of analytical procedures
 - **Are methods capable of distinguishing each active ingredient in a combination product?**
 - **Absence of possible interference (actives and degradation products)?**
 - Batch analyses
 - Characterization of impurities
 - **Any new degradation products? Are they qualified?**
 - Justification of specification(s)
- P.6 Reference Standards or Materials

Module 3

3.2.P Drug Product

- P.7 Container Closure System
- P.8 Stability
 - Stability summary and conclusion
 - Postapproval stability protocol and stability commitment
 - Stability data
 - **Sufficient for proposed expiration dating period?**
- Also – Appendices and Regional Information (e.g., Executed Batch Records, Environmental Assessment, and Labeling)

Additional Suggestions for 505(b)(2) CMC Section

- Consider all relevant FDA and ICH guidelines (e.g., impurities, residual solvents); provide justification for any alternative approaches
 - Guidances (including ICH):
[http://www.fda.gov/Drugs/
GuidanceComplianceRegulatoryInformation/
Guidances/default.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)
- Consider QbD approaches – see ICH Q8, Q9, and Q10.

Summary

- Section 505(b)(2) of the FFD&C Act permits an applicant to rely (at least in part) on studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.
- Complete CMC information must be submitted for the drug substance(s) and the drug product – to support the quality of the proposed drug product for marketing

Thank you!

Any CMC questions, comments, concerns:

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General 505(b)(2) questions:

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