Strategies for IND Filing Success: Chemistry, Manufacturing and Controls

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Presentation Outline

- Background
- High Level CMC Contents Overview
- CMC Detail vs. Clinical Development Stage
- Summary
- References

Background

FDA Regulation of Clinical Trials

With ….the Prescription Drug User Fee Act of 1992 (PDUFA) review action performance goals, and the resulting significant declines in mean and median time ….attention has turned to increasing the efficiency of other components of the drug development process….. One part of IND regulation of particular interest …. is the regulation of the initial testing of drugs in humans (*i.e.*, Phase 1 trials).

This guidance* clarifies requirements for data and data presentation in 21 CFR 312.22 and 312.23 related to the initial entry into human studies in the United States of an investigational drug, including well-characterized, therapeutic, biotechnology-derived products. Present regulations allow a great deal of flexibility in the amount and depth of various data to be submitted in an IND depending in large part on the phase of investigation and the specific human testing being proposed…..

* Guidance For Industry: Content and Format for INDs for Phase 1 Studies of Drugs Including Well Characterized Therapeutic, Biologically Derived Products, CDER, CBER, November 1995

Guidances (Drugs)

- The category "Chemistry, Manufacturing and Controls" has been renamed Pharmaceutical Quality/CMC
  - The guidance document entitled "Submitting Documentation for the Manufacturing of and Controls for Drug Products" was withdrawn *4/14/2015.*
- This guidance was withdrawn because many of the recommendations were obsolete and have been more recently addressed in FDA and ICH guidance documents, including, but not limited to;
  - Content and Format for INDs for Phase 1 Studies of Drugs Including Well Characterized Therapeutic, Biologically Derived Products
  - INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information
  - Q2A Text on Validation of Analytical Procedures
  - Q2B Validation of Analytical Procedures: Methodology
  - Q3C Impurities: Residual Solvents
  - Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
  - M4: The CTD -- Quality

Disclaimers

- This presentation:
  - Is applicable to small chemical entities
  - Excludes novel therapeutic chemical entities
  - Excludes biologically derived therapeutic agents
  - Excludes botanical therapeutic agents
  - Excludes therapeutic agents derived from natural sources

High Level CMC Contents Overview

Pharmaceutical Quality/CMC

Drug Substance Information Needed

- A description of the drug substance, including its physical, chemical, or biological characteristics
- The name and address of its manufacturer
- The general method of preparation of the drug substance
- The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance
- Information to support the stability of the drug substance during the toxicology studies and the proposed clinical trial(s)

Pharmaceutical Quality/CMC

Drug Product Information Needed

- List of components, including alternatives for inactive compounds used to manufacture investigational drug product, including those intended to appear in the drug product and those which may not appear, but are used in the manufacturing process
- Where applicable, the quantitative composition of the investigational new drug product, including any reasonable variations that may be expected during the investigational stage
- The name and address of the drug product manufacturer
- General description of manufacturing & packaging procedures appropriate for product
- The limits & analytical methods for identity, strength, quality, and purity of the drug product
- Information for stability of drug substance during the toxicological studies and proposed clinical trial
- General description of composition, manufacture, control of any placebo to be used
- A copy of all labels and labeling to be provided to each investigator

CMC Detail vs. Clinical Development Stage

CMC Detail Increases As Clinical Development Progresses
Emphasis on Patient Safety

The amount of information submitted depends on the stage of investigation, testing proposed in humans, duration of testing and whether the information is safety related. The Guidances identify information that would be presented as information amendments & annual updates. An IND for each phase of investigation must include sufficient CMC information to ensure identity, strength, potency, quality & purity of the drug substance and drug product.

Phase I

- Sponsor states if 1) chemistry of drug substance or drug product, or 2) manufacturing of drug substance or drug product pose any potential human risk. If so, this is discussed along with steps to monitor them. Sponsors should describe chemistry/manufacturing differences between drug product for clinical use & drug product used in animal toxicology trials that formed the basis for sponsor's conclusion it's safe to proceed with the clinical study.

Phase II

- As sponsor documents its product development program, more detailed information is used to establish correlations between data generated in IND studies & the to-be-marketed product & support process controls & specification justification in the NDA. Sponsor carefully assesses changes in manufacturing process/formulation throughout clinical development to determine if changes directly or indirectly affect the safety of the product.

Phase III

- FDA encourages sponsors to meet with the CMC review team before the initiation of Phase 3 clinical trials to discuss issues and protocols that might affect the approvability of the NDA.

Degree of Drug Substance Detail Required

Information	Clinical Development Stage		
	Phase 1	Phase 2	Phase 3
Physical, chemical & biological description	Brief description & some evidence to support its proposed chemical structure	Details on chemical structure to help predict structure of possible metabolites. For peptides; amino acid sequence & peptide map. For DNA products; nucleic acid sequence, DNA melting points & side-chain modifications	Specific details including pKa, isoelectric point, hygroscopicity, crystallinity vs. amorphous, particle size, melt point, chirality, biologic properties.
Manufacturer name & address	Full street address of the manufacturer of the clinical trial drug substance	Addition, deletion or change of any manufacturer of DS used in Phase 1.	List of all firms related to DS manufacture including any contract facilities for testing or release
Method of preparation	Brief description of manufacturing process, reagents, solvents, and catalysts used. A detailed flow diagram to present the information.	Updated flow diagram for synthesis or manufacturing process. Need stereo-chemical info on starting/intermediate material. Equipment & monitoring controls. For sterile drugs need more details on sterilization process.	Synthesis/manufacturing flow diagram including batch size, solvent/reagent ratios, process controls, operating conditions, control of intermediates & impurities, validation of sterilization.
Acceptable limits & analytical methods to assure identity, strength, quality, purity	Brief description of test methods, proposed acceptable limits, supported by simple analytical data, for clinical trial material. COA. Validation not needed.	CQLs refined based on more stability batches. Description & validation od non-compendia methods. Impurities qualified. CC description needed.	Detailed list of all tests of batch release of all CTM. Detail on ref. standards, impurities / microbial limits.
Support for stability during toxicology or clinical studies	Brief description of stability study & test methods to monitor DS stability. Tabular data based on representative material is ok. Detailed stability data or stability protocol not needed.	Acceptance criteria and quality monitoring now based on degradation. Stability indicating methods needed.	Stress and accelerated data for multiple lots needed in the actual CC that will be in the NDA. Detail of degradation paths needed.

Degree of Drug Product Detail Required

Information	Clinical Development Stage		
	Phase 1	Phase 2	Phase 3
Components & inactive compounds used in manufacture	A list of no more than 1-2 pages of written information should be submitted. The quality (*e.g.,* NF, ACS) of the inactive ingredients should be cited.	All components used in manufacture of drug product, identified by name with reference to the quality standard (NF) with numeric values	Full characterization of any non-compendium excipients and/or DMF reference.
Quantitative composition and potential for variation	Brief summary of composition of the investigational new drug product is needed. Usually, information on component ranges is not necessary	A Representative batch formula with quantitative information for every component in the formula is needed.	Any changes from Phase 2.
Manufacturer name /address	The full street address(es) of the manufacturer(s) of the clinical trial drug product should be submitted.	Addition, deletion or change of any manufacturer of DS used in Phase 1 including contract facilities for manufacturing or release.	Addition, deletion or change of any manufacturer of DS used in Phase 2 plus names for stability, QC release, packaging and labeling
Description of manufacturing & packaging procedures	A diagrammatic presentation &brief written description of manufacturing process is needed, including sterilization process for sterile products. Flow diagrams are suggested to present information.	Flow diagram with step by step manufacturing process details. Detail can be at the "unit operation" level not at the step by steps within a unit operation.	Updated flow diagram showing if reprocessing is allowed. Describe packaging/labeling. For sterile products, details of validation
Acceptable limits/analytical methods to assure identity, strength, quality, purity	Brief description of proposed limits & test methods. Example: For sterile products, sterility and non-pyrogenicity. A COA of the clinical batch. Validation data and established specifications not needed	Physicochemical tests (assay, impurities, viscosity, particle size, content uniformity, dissolution) and microbiological tests (sterility, pyrogen, bacterial endotoxin, preservative effectiveness, etc.) and limits needed.	Degradation products & impurities identified, qualified & specified. Limits established from stability data & safety profile.
Support for stability during toxicology or clinical studies	Brief description of stability study & test methods for stability of drug product packaged in the proposed container/closure system & storage conditions needed. Preliminary tabular data needed	Any changes from Phase I. Stability data from CTM, multiple batches & different batch sizes. Stability indicating assays to deal with CC related degradation.	Stability data from stress/ accelerated studies of CTM in respective CC
Composition/manufacture /control of placebo	Diagrammatic, tabular, brief written information	Any changes from Phase I.	Any change since Phase 2.
Copy of all labels provided to investigators	Per 21 CFR 312.6(a). Caution: New Drug - Limited by Federal (United States) law to investigational use.	Any changes from Phase I.	Any change since Phase 2.

Summary

- The content of the CMC section of the IND evolves, as product development evolves to better meet the clinical needs of the patient
- The amount of detail required in the CMC section needs to be appropriate to address relevant safety concerns to the patient over the duration of the clinical study
- Sponsors should interact with FDA at each clinical development stage so that the quality of data is progressing in line with what will be needed to obtain an approved NDA

References

- INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information
- Q2A Text on Validation of Analytical Procedures
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