Quality Issues for Clinical Trial Materials:
The Chemistry, Manufacturing and Controls (CMC) Review

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Outline

• IND Guidance Sources
• Pharmaceutical Quality
• CMC Requirements for INDs
• CMC Safety Concerns
• Impurities
• Other Considerations (QbD)
• Summary
IND Guidance Sources

• Food Drug and Cosmetic Act
• Code of Federal Regulations (Title 21)
  – 21 CFR 312 (IND content and format)
  – 21 CFR 210 and 211 (CGMP)
• Guidance
  – FDA
  – ICH
Investigator Brochure CMC

21 CFR 312.23(a)(5) Investigator’s brochure.

If required under § 312.55, a copy of the investigator’s brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.
FDA IND Guidance

• Phase 1 (http://bit.ly/IND-Phase-1)
• Phase 2 & 3 (http://bit.ly/IND-Phase2-3)
• Meetings (http://bit.ly/IND-meetings)
• MaPP 6030.1 (http://bit.ly/IND-MaPP)
• Exploratory IND (http://bit.ly/Expl-IND)
• GMP for Phase 1 (http://bit.ly/IND-cGMP)
Guidance for Industry: CGMP for Phase 1 Investigational Drugs (2008)

- Frequent questions about GMP expectations for Phase 1 trial materials; clear need for guidance
- Developed by Agency workgroup (CDER, CBER, ORA) composed of compliance staff, CMC reviewers, and investigators
- FDA’s desire to ensure appropriate quality for early clinical trial material, without impeding drug development
- Articulates FDA’s intent to implement an incremental approach to CGMP compliance for clinical investigational products
- FDA Guidance issued in 1991 “Preparation of Investigational New Drug Products (Human and Animal)” (reprinted November 1992) still applies to Phase 2 and Phase 3 clinical trial materials
Meetings

• Pre-IND Meetings

• EOP2 Meetings
  – Ensure that meaningful and adequate data are generated during Phase 3 studies
  – Identify safety issues, scientific issues and/or potential problems and address/resolve them prior to initiating Phase 3 studies
  – Identify potential roadblocks that could affect review of marketing application
  – Discuss and agree on plans/protocols relative to:
    • Regulations, guidances, and FDA policy
    • Quality by Design (QbD) approaches, if used

• Pre-NDA Meetings
  – Generally focusing on filing and format issues at least 6 months prior to NDA submission
  – Discussion of any problems that can lead to refuse-to-file recommendation or hinder the review process
Drug Substance and Drug Product

• Drug Substance (Active Pharmaceutical Ingredient, API)
  – An active ingredient, intended for incorporation into a finished dosage form, that meets the statutory definition of a drug (i.e., that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body)

• Drug Product
  – A finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally but not necessarily in association with one or more other ingredients

21 CFR 314.3 Definitions
The challenge for the Quality review and inspection for a New Drug Application is to assure that the characteristics and performance of the clinical batches will be replicated consistently in the commercial batches.
IND Regulation

• 21 CFR 312.23(a)(7)(i)
  – As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product..............
  
  – ........... sufficient CMC information to assure the proper identification, quality, purity and strength of the investigational drug
Identity

• The structure of the Drug Substance (API) must be proven and controls must be used in the manufacturing process to ensure that the same structure is obtained in every batch.

• The types of techniques or combination of techniques that may be required to fully elucidate the structure depends on the nature of the drug substance.
Strength (Potency/Assay)

The drug product needs to contain the required amount of drug substance

• Assay of the Drug Substance
  – Validated stability-indicating assay or bioassay
• Assay of the Drug Product
  – Validated stability-indicating assay or bioassay (assay needs to be selective for the drug substance without interference from excipients, impurities, or degradants)
• Well-controlled manufacturing processes
• In-Process Blend Uniformity
• Uniformity of Dosage Units
• Container/Closure (Adsorption/Absorption)
• Stability (Expiration Dating Period)
Purity

- Chemical purity
  (process impurities, degradation products, leachables from container closure system, etc.)

- Microbiological purity
  (microbial limits; absence of specific microorganisms, etc.)
CMC Regulatory Requirements

[21 CFR312.23(a)(7)]

• Regulations emphasize the graded nature of CMC information needed as drug development progresses under an IND.

• The amount of information needed depends on:
  – Phase of investigation
  – Dosage form
  – Duration of study
  – Patient population
  – Amount of information otherwise available

• The emphasis in an initial Phase 1 CMC submission should generally be placed on providing information that will allow evaluation of the safety of subjects in the proposed study.
Drug Substance Requirements for INDs

• Description and characterization
• Manufacturer (name, address, contact information)
• General method of preparation/synthesis
• Specification (tests, analytical procedures and acceptance criteria)
• Batch analysis data for clinical trial batch
• Stability (through end of clinical trial)
Drug Product Requirements for INDs

• Components
  – Novel excipients may require additional information
• Quantitative composition
• Manufacturer (name, address, contact information)
• Description of manufacturing and packaging process
• Container/closure system
• Specification (tests, analytical procedures and acceptance criteria)
• Stability (through end of clinical trial)
Other Drug Product Requirements

• Labels and labeling – mock-up labels
  – Caution statement that reads: “Caution: New Drug Limited by Federal (or United States) law to investigational use.”

• Environmental Assessment
  – Claim for a categorical exclusion

• Placebo information
CMC Safety Concerns

• Potential safety issues for drug substance
  o Not well characterized
  o Not well controlled (e.g. assay, impurities, residual solvents)
  o Impurities that are structural alerts (e.g. genotoxic)
  o Lack of stability (e.g., degradation impurities) to support clinical duration
  o Lack of comparative assessment clinical vs. pre-clinical drug substance so as to link safety.

• Potential safety issues for drug product
  o Formulation – composition (such as excipients)
  o Dosage form and route of administration
  o Controls/specifications (safety)
  o Stability of formulation, packaging compatibility, in-use, etc.
CMC Safety Concerns (potential “hold” issues)

• Generally
  – Impurities
  – Overdose

• For parenteral products
  – Sterility
  – Endotoxins
  – Particulates
What is an impurity?

– Any component of the new drug substance that is not the chemical entity defined as the new drug substance (ICH Q3A)

– Any component of the drug product that is not the drug substance or an excipient in the drug product (ICH Q3B)
Drug Substance Impurities

• Drug substance impurities
  – Organic impurities (process- and drug related, e.g., starting materials, by-products, intermediates, degradation products, reagents, catalysts)
  – Inorganic impurities (heavy metals or other residual metals, inorganic salts)
  – Residual solvents, polymorphic forms, enantiomeric impurities, extraneous contaminants

• Drug product impurities
  – Degradation product of the drug substance
  – Reaction product of the drug substance with excipient and/or with immediate container/ closure system
Impurities More Toxic than Drug

Desmethylprodine, an opioid analgesic

causes chronic irreversible Parkinsonian symptoms

MPTP

Quality by Design - QbD

Design product with patient in mind:
Quality Target Product Profile (QTPP)

Understand Product:
Critical Quality Attributes (CQA)

Rational Design of Manufacturing Process

Understand Process
Manufacturing Parameters ↔ CQA
Mapping the Linkage

Inputs:
- M1
- M2
  Material Attributes
- P1
- P2
- P3
  Process Parameters

Outputs:
- CQA1
- CQA2
- CQA3
  Critical Quality Attributes

Relationships:
- CQA1 = function (M1)
- CQA2 = function (P1, P3)
- CQA3 = function (M1, M2, P1)
Drug Product Specification

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Acceptance Criteria (typical values)</th>
<th>Analytical Procedure (for example)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>Matches Standard</td>
<td>IR or HPLC/UV</td>
</tr>
<tr>
<td>Appearance</td>
<td>Color, Imprint</td>
<td>Visual</td>
</tr>
<tr>
<td>Assay</td>
<td>90-110%</td>
<td>HPLC</td>
</tr>
<tr>
<td>Dose Uniformity</td>
<td>Statistical Criterion (USP)</td>
<td>HPLC or Weight</td>
</tr>
<tr>
<td>Release from Dosage Form</td>
<td>80% in 15 or 30 minutes</td>
<td>Stirred Aqueous Vessel</td>
</tr>
<tr>
<td>Impurities (Related Substances)</td>
<td>&lt;1% to few %</td>
<td>HPLC</td>
</tr>
<tr>
<td>Microbial Limits Or Sterility</td>
<td># of total aerobes and fungi per gram Pathogen (-)</td>
<td>Growth in special media</td>
</tr>
<tr>
<td>Water Content</td>
<td>Few %</td>
<td>Chemical or wgt. loss</td>
</tr>
<tr>
<td>Preservative Content</td>
<td>NLT 75% of Initial</td>
<td>HPLC</td>
</tr>
</tbody>
</table>
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<tr>
<td>Assay</td>
<td>98-102%</td>
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</tr>
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<td>Color</td>
<td>Visual</td>
</tr>
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<td>Impurities (Related Substances)</td>
<td>&lt;1% to few %</td>
<td>HPLC</td>
</tr>
<tr>
<td>Inorganic Impurities</td>
<td>Heavy Metals (ppm)</td>
<td>Spectroscopy</td>
</tr>
<tr>
<td></td>
<td>Na, etc ~ %</td>
<td>Residue on Ignition</td>
</tr>
<tr>
<td>Residual Solvents</td>
<td>ppm to 0.5%</td>
<td>Head-space GC</td>
</tr>
<tr>
<td>Particle Size</td>
<td>Case-by-case</td>
<td>Sieve, Laser Diffract.</td>
</tr>
<tr>
<td>Solid-State Form</td>
<td>Conforms/limit</td>
<td>Powder X-Ray; IR</td>
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CMC Efficacy Concerns

- Generally not a reason for a “clinical hold”
- Assay uncertainty
- Uniformity of content
- Bioavailability
Rifampin Bioavailability

**Particle size**

- Standard product

**Formulation/manufacture**

- Standard product
- Process change
- Excipient change
- Same process
- Process change

*R. Cavenaghi, Bull Int Union Tuberc Lung Dis 1989 Mar; 64(1):36-7*
Use of Foreign Comparators in Clinical Trials*

Sample comment:

“The use of FDA-approved drug products provides assurance of drug quality. Where this is not possible and local products are used, documentation should be provided to show that the drug product is comparable in quality to the US product. Depending on the drug product, this could involve, for example, comparing impurity and dissolution profiles, and content uniformity.”

* Pre-IND approach recommended
Excipients – Quality Considerations

- Suitability for intended use (target organ/tissue)
- Functionality
- Compatibility with drug substance
- Safety/performance issues
- Source (USP/NF; FDA Inactive Ingredients Database)
- Excipients of Human or Animal Origins
- Novel (new) Excipients*

*(1) Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients; (2) USP General Chapter <1074>
Container Closure System

- The sum of packaging components that together contain, protect, and deliver the dosage form
- IND should include a brief description of:
  - The packaging components
  - The assembled packaging system
  - Any precautions needed to ensure the protection and preservation of the drug substance and the drug product during the use in the clinical trials
Stability

• 21 CFR 312.23(a)(7)(ii): …stability data are required in all phases of the IND to demonstrate that the DS and DP are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation

• The amount of data will depend upon the duration of the proposed clinical study
Use of Stability Data

• To support investigational studies
• To ensure that the quality and safety of the investigational product is maintained throughout the clinical trial period
• To obtain impurity profile of the batches used during non-clinical toxicological studies
Expiration Dating Period

- Expiration dating period is not required for the investigational materials.
- Reconstituted products are required to have a “use by” date.
- CFR 211.137 (g). “Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product.”
Clinical Trial Supplies*

- Examine container integrity on receipt
- Confirm label’s 21 CFR 312.6 compliance
- Store at recommended conditions

Document:
- Receipt and storage
- Condition of product on receipt
- Dosing (including e.g. date & time, lot#, etc)
- Reconciliation of all product at study conclusion
- Records kept on-site

*See International Conference on Harmonisation of Technical Requirements for Registration Of Pharmaceuticals for Human Use Guidance E6, “Guideline for Good Clinical Practice”
Summary

• Sufficient CMC information should be provided in an IND to assure identity, quality, purity and strength of the study drug

• The level of CMC information increases as development progresses

• CGMP should be applied - Phase 1 drugs do not need full CGMP but do need good manufacturing controls

• Critical CMC safety issues (including impurities) should be identified - safety concern is the primary reason for placing an IND on clinical hold based on CMC section

• Other quality issues should be considered and evaluated for INDs

• Recommendations of ICH/FDA guidances and input from FDA are helpful during drug development
Thank you!