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Investigator Brochure: CMC Considerations

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Presentation Overviews

- Introduction to CMC requirements and the investigator brochure
- Summary of CMC information included in the investigator brochure
- Product and clinical development parallels
- Available guidance documents
CMC IND Requirements

- 21 CFR* 312
  - Format and content
- 21 CFR 211
  - Expiry date for reconstituted products

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.
21CFR Information for Investigators

- 312.23(a)(5) *Investigator's brochure*. If required, containing the following information:
  - (i) A brief description of the drug substance and the formulation, including the structural formula, if known.
  - (ii-v) Information related to safety & efficacy
- 312.55 ... The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations...
- 312.32(c) *IND safety reports* ... The sponsor shall notify FDA and all participating investigators in a written IND safety report...
What is behind the CMC information included in the IB at phase 1

- Investigator brochure has very little CMC information relative to the enormous amount of work that has gone into developing and preparing a product for phase I studies.
- Understood that product has been manufactured in a way that it will be safe for first in human use (detailed elsewhere in the IND).
What is behind the CMC information included in the IB at phase 1

Expectations (or lack thereof) for products going into phase 1 studies:

- **Product is considered to be in its infancy**
  - No expectation for efficacy
  - No expectation for product specifications

- **Product will be safe!**
  - This will be supported by
    - nonclinical studies
    - initial manufacturing strategy
    - characterization of raw materials and substrates
    - quality control profile of investigational materials
    - preliminary stability studies
CMC information

Summary Section:

- Simple description of the product and disease indication
- What is contained in the product
  - Active ingredient
- Summary of critical nonclinical studies
  - Animal models used
  - Summary of study results
  - Any previous human studies
CMC information

Introduction

- More detailed description of product
- Product X consists of ....
  - Describe product qualities that are critical for the intended indication
  - As an example - for vaccines:
    - What are the antigenic properties of the product
    - What are the attenuating mutations and how do they affect phenotype
    - What are the properties of the antigen and how are they presented for inactivated or subunit vaccines
CMC information
Physical, Chemical, and Pharmaceutical Properties and Formulation

- Product description –
  - General description of the investigation product

- Product formulation and filling –
  - What are the components of the final product?
    - Active ingredients
    - Ingredients in final formulation including buffers, adjuvants, stabilizers
  - How is the product presented or supplied?
    - Vial vs. Syringe
    - Lyophilized with diluent
    - Single vs. multidose
CMC information

Physical, Chemical, and Pharmaceutical Properties and Formulation (cont’d)

- Route of Administration and Dosing Schedule –
  - Oral vs. parenteral
  - Administration schedule

- Dose levels and volumes –
  - What amount of product will be administered (dose/potency)
  - What volume of product will be administered

- Storage and Handling –
  - Description of proper storage and handling

- Product Manufacturer
CMC information

Nonclinical studies – details of studies performed to:

- Assess functionality of product, including:
  - attenuation, immunogenicity, efficacy
    - In relevant animal models if available
    - Otherwise, in 2nd best model

- Assess safety data in animals
  - Toxicology studies
Other CMC information included in the IND

- Background on product development
  - Scientific development
  - Manufacturing process
- Details on characterization of raw materials
- Details of the manufacturing process
- Details of the quality control testing done to ensure product safety
- Details of future development as clinical trials proceed towards licensure
CMC and the IB after phase 1

- Change in manufacturing scale
- Initial identification of critical process parameters
- Assay and process validation
  - Leads to establishment of preliminary product specifications
- Definition of a dose
  - Establishment of a well defined potency test
CMC and the IB through phase 3 and licensure

- Commercial manufacturing scale is defined
- The manufacturing process is validated
- Product specifications are established
- Clinical consistency is linked with manufacturing consistency
  - Product behavior in the clinic studied using multiple lots produced using final process
- Potency is linked with efficacy – final definition of a “dose”
Changes to CMC section of IB

- As clinical development continues some changes may be:
  - Change in dosing and route of administration
    - Data from phase 2 studies
  - Change in formulation
    - Data from changes in manufacturing
  - Inclusion of additional nonclinical data
    - Data requested after initiation of phase 1 study
      - Additional product characterization data
  - Change in antigen or product content
    - This type of change may require a new IND
CMC reflected in the IB

- Despite the brevity of information actually included in the investigator brochure there is an amazing amount of work and effort behind the information included.

- The CMC data in the investigator brochure implies that all materials used in clinical trials are initially safe and ultimately safe, potent, and efficacious.
IND Guidance Sources

- Food Drug and Cosmetic Act
- Code of Federal Regulations (Title 21)
- Guidance
  - FDA
  - ICH
    International Conference on Harmonisation
Guidances

1. Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products - Final 7/1997
2. Changes to an Approved NDA or ANDA - Final 4/2004
3. Changes to an Approved NDA or ANA; Specifications - Use of Enforcement Discretion for Compendial Changes - Final 11/2004
5. Container Closure Systems for Packaging Human Drugs and Biologics – Final 5/1999
7. Drug Master Files Current DMF Information - Final 9/1989
Guidances

- 10. INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information - Final 5/2003
- 11. IND Meetings for Human Drugs and Biologics Chemistry, Manufacturing, and Controls Information - Final 5/2001
ICH Documents

- Q1A(R2) Stability Testing of New Drug Substances and Products - Final 11/2003
- Q1B Photostability Testing of New Drug Substances and Products - Final 11/1996
- Q1E Evaluation of Stability Data - Final 6/2004
- Q2A Text on Validation of Analytical Procedures - Final 3/1995
- Q2B Validation of Analytical Procedures: Methodology - Final 5/19/1997
- Q3A(R) Impurities in New Drug Substances - Final 2/10/2003
- Q3B(R) Impurities in New Drug Products - Final 11/2003
- Q3C Impurities: Residual Solvents - Final 12/24/1997
ICH Documents

- Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of DNA Derived Protein Products - Final 2/1996
- Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products - Final 7/1996
- Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products; Availability - Final 9/21/1998
- Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process - Final 6/2005
ICH Documents

- Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products - Final 8/1999
- Q7 A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients - Final 8/2001
- Q8(R2) Pharmaceutical Development - Final 8/2009
- Q9 Quality Risk Management - Final 96/1/2006
- Q10 Quality Systems - 4/8/2009