Guidance on CMC for Phase 1 and Phases 2/3 Investigational New Drug Applications

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Disclosures

- I am currently employed as an Executive Director in Global CMC in Pfizer Inc.
- I worked at the U.S. Food and Drug Administration (FDA) in 1978 till 2003. I was the Deputy Director in the Office of New Drug Chemistry, CDER.
- The following are my views and not necessarily the views of the Food and Drug Administration Alumni Association (FDAAA), the FDA, or Pfizer
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Outline

- What is an IND and how it is regulated in the U.S.?
  - Study objectives during different phases of IND
  - Amount of CMC information varies depending on phase, etc.
  - Why full CMC information is not required in Phase 1 IND?
  - CMC amendments and annual reports
- CMC/GMP related guidances
  - Drug substance information for Phase 1 and Phase 2/3
  - Drug product information for Phase 1 and Phase 2/3
- CMC differences between IND and NDA
- FDA meetings with IND sponsors or NDA applicants
- CGMP requirements for Phase 1 IND
- Summary

What is an IND and how is it regulated?

- Law: FD&C Act 505(i) exempts a drug intended solely for investigational use by qualified experts from filing a New Drug Application (NDA) or ANDA
  - Application for this exemption is called an Investigational New Drug Application (IND)
  - Unlike other drug applications, INDs are neither approved nor disapproved. The clinical studies are either permitted to proceed or are placed on clinical hold for safety reasons
  - After a new IND is filed, there is a mandatory a 30-day safety waiting period to allow the FDA 30 days to make a safety assessment

What is an IND and how is it regulated? (cont'd)

- Major revision to IND regulation in 1987: The objectives were to establish a more efficient process
  - *To encourage innovation and drug development while continuing to assure safety of test subjects in Phase 1 by:*
    - Focusing FDA's attention on protecting safety of test subjects
    - Giving greater freedom to sponsors to design, revise, and implement clinical studies
  - *To ensure efficient review of subsequent NDA by:*
    - Facilitating close consultation between sponsors and FDA prior to Phase 3 and helping design acceptable major trials to support marketing approval
  - *To benefit the consumer by:*
    - Enhancing earlier availability of safe and effective drugs post-NDA

Study Objectives during the different IND Phases

- Phase 1: Initial introduction of a new drug into humans
  - Closely monitored, typically 20-80 patients or normal subjects
  - To study metabolism and pharmacological actions of drug
  - To detect side effects associated with increasing doses
  - Look for early evidence of effectiveness
- Phase 2: Limited, controlled clinical studies
  - Closely monitored, usually several hundred subjects
  - To obtain preliminary data on effectiveness of the drug
  - To determine common short-term side effects and risks
- Phase 3: Expanded, controlled and uncontrolled trials
  - Usually several hundred to several thousand subjects
  - To gather additional effectiveness and safety information
  - To provide an adequate basis for extrapolating results to general population and in supporting that information in the labeling

FDA IND Regulations

- Regulation: 21 CFR 312
  http://www.access.gpo.gov/nara/cfr/waisidx_03/21cfr312_03.html
  - INDs categories
    - Commercial IND (sponsored by drug companies)
    - Non-commercial IND (sponsored by individual investigators)

- CMC regulation: 21 CFR 312.23(a)(7)(i)
  - "…. Although in each phase of the investigation sufficient information is required … to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed will vary with the phase …, the proposed duration …, the dosage form, and the amount of information otherwise available"

FDA IND Regulations (cont'd)

- CFR 312.31: Information Amendments (IA)

  (a) "A sponsor shall report in an information amendment essential information on the IND…

  Examples of information requiring IA include:"

  (a)(1) "New toxicology, chemistry, or other technical information;"

- CFR 312.33: Annual Reports (AR)

  (b)(7) "A summary of any significant manufacturing or microbiological changes made during the past year."

CMC IND Information Submitted

- Amount of information needed depends on:
  - Phase of the investigation
  - Known or suspected risks
  - Novelty of the drug
  - Previous studies conducted
  - Dosage form/route of administration
  - Nature & extent of clinical study
  - Patient population

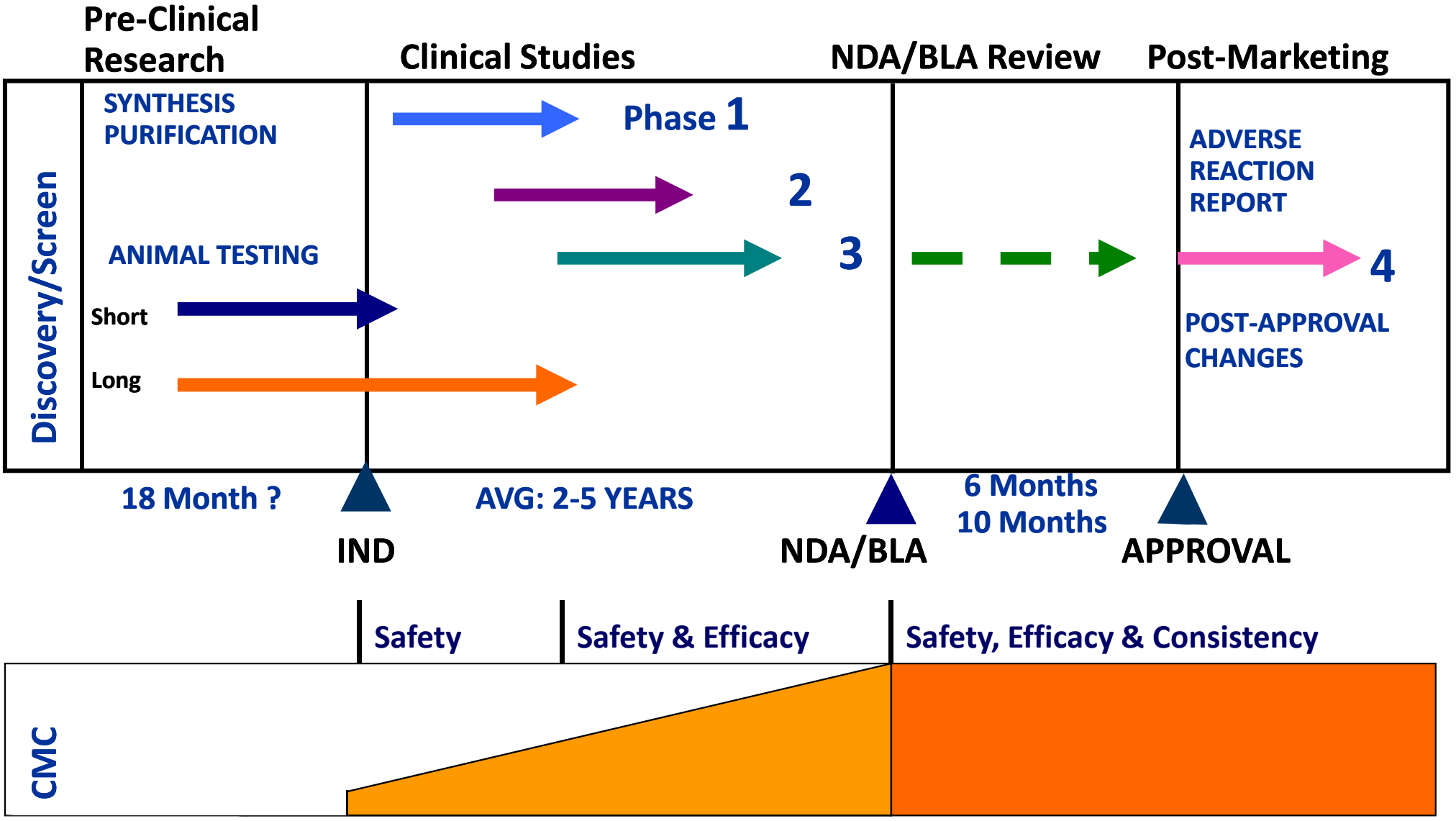
CMC IND Amendments and Annual Reports

- Amendments are submitted under the same IND without a 30-day waiting period
- Amendments are for CMC changes that may affect safety, e.g.,
  - Change in the method of sterilization
  - Change in the container closure system affecting product quality
  - Change in the synthesis resulting in different impurity profiles
  - Change from synthetic to biological source (human or animal) of a drug substance
- Other CMC changes or updates are reported in annual reports

CMC/GMP Related FDA Guidances

- "Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products" (1995)
- "Formal Meetings Between the FDA and Sponsors or Applicants" (2009)
- "IND Meetings for Human Drugs and Biologics - Chemistry, Manufacturing, and Controls Information" (2001)
- "INDs for Phase 2 and Phase 3 Studies - Chemistry, Manufacturing, and Controls Information" (2003)
- "CGMP for Phase 1 Investigational Drugs" (2008)

CMC and Drug Development Cycle



Why full CMC Information is not required in Phase 1 INDs

- Safety is the main concern which is addressed with pharm/tox data
- Drug substance has been tested, thus impurity profile and potency are known in animals before given to human
- Generally a small number of patients in Phase 1
- Trial duration is normally short for Phase 1
- Clinical trials are conducted under a controlled setting where adverse events can be monitored
- There is continuous regulatory oversight and review throughput the development cycle
- Limited number and/or size of batches have been manufactured
- Formulation, analytical procedures, and manufacturing process are being refined and improved
- Drug substances and products are manufactured according to CGMP, even though Phase 1 IND drugs are exempt from CGMP requirements

Drug Substance Data for Phase 1

- Reference to current edition of USP-NF, if applicable
- Authorized reference to a DMF, if applicable
- Brief description, including physical, chemical, and biological properties
- Sufficient evidence to support chemical structure
- Manufacturer identified
- Method of preparation**
  - Brief description of manufacturing process
  - List of reagents, solvents, and catalysts
  - Flow diagram – suggested

** More information may be needed for well-characterized, biotechnology-derived drugs and drugs extracted from human or animal sources

Drug Substance Data for Phase 1 (cont'd)

- Specification
  - Proposed acceptance criteria supported by analytical data from clinical trial material
  - Brief description of analytical procedures
  - Certificate of Analysis (COA) - suggested
- Stability
  - Brief description of stability study and analytical procedures used
  - Preliminary stability data (tabular) may be submitted
  - Detailed stability data not needed
  - Stability protocol not needed

Drug Product Data for Phase 1

Summary report containing the following items:

- Components and composition
  - List of all components used in the manufacture of the investigational drug
  - Quality of inactive ingredients (e.g., USP/NF)
  - Novel excipients - additional CMC information may be needed
  - Brief summary of composition
  - Component ranges not needed
- Manufacturer identified
- Method of manufacturing and packaging
  - Brief description (sterilization process for sterile products, if utilized)
  - Flow diagrams - suggested

Drug Product Data for Phase 1 (cont'd)

- Specification
  - Proposed acceptance criteria supported by analytical data from clinical trial batch
  - Brief description of analytical procedures
  - COA of the clinical batch - suggested
  - Established specification or methods validation not needed
- Stability
  - Brief description of stability study and analytical procedures used
  - Preliminary tabular data - may be submitted
  - Detailed stability data not needed
  - Stability protocol not needed

Drug Substance Data for Phases 2 & 3

- Characterization and Description

  Phase 2

  - Safety updates on the information provided for Phase 1
  - More detailed description of the configuration and chemical structure for complex organic compounds

  Phase 3

  - Complete description of the physical, chemical and biological characteristics and supporting evidence to elucidate and characterize the structure

- Manufacturer

  Phase 2 and 3

  - Addition, deletion, or change of any manufacturer during Phase 1
  - Also, include contract laboratories for quality control and stability testing

Drug Substance for Phases 2 & 3 (cont'd)

- Synthesis/Method of Manufacture and controls
  - Starting materials (more information for Phase 3)
  - Safety updates on reagents, solvents, auxiliary materials, and proposed changes identified during earlier phase(s) (more information for Phase 3)
  - Synthetic and manufacturing process - general description (updated from a safety perspective, if changed) for Phase 2 and detailed description for Phase 3
  - Flow diagram
  - In-process controls
  - Reprocessing and pertinent controls - Safety related information for Phase 2 and description for Phase 3

Drug Substance for Phases 2 & 3 (cont'd)

- Reference standard established in both phases
- Specification

Phase 2 and 3

- Complete description of the analytical procedure and supporting validation data ready for submission at phase 3

Phase 2

- Any change in the tentative specification from earlier phase(s)
- List of the test method used
- Test results, analytical data and COA of clinical trial materials since original IND filing

Drug Substance for Phases 2 & 3 (cont'd)

- Specification

  Phase 3

  - Impurities should be identified, qualified, and quantified, as appropriate
  - Suitable limits based on manufacturing experience should be established
  - Detailed list of tests performed
  - General description of the USP analytical procedures
  - Complete description of the non-USP analytical procedures with validation data
- Container/closure
  - Brief information for phase 2 and more detailed information for Phase 3

Drug Substance for Phases 2 & 3 (cont'd)

- Stability:

  Phase 2

  - Stability-indicating method
  - Stability protocol
  - Preliminary stability data on a representative material
  - All stability data for the clinical material used in Phase 1

  Phase 3

  - Detailed stability protocol
  - Detailed stability data
  - Stress studies - should be conducted

Drug Product Data for Phases 2 & 3

- Components/composition/batch formula:
  - Any change during earlier phase(s)
  - Established names and compendial status for components, if any
  - Quantitative composition per unit dose
  - Batch formula
  - List components used and removed during the manufacturing of the drug product for Phase 3
  - The formulations of certain drug product delivered by devices (e.g., MDIs, DPIs, and nasal spray) should be similar to that intended for the marketed drug product

Drug Product for Phases 2 & 3 (cont'd)

- Specifications for components
  - Active: Any change during earlier phase(s)
  - Compendial inactive: Specify quality, if changed
  - Noncompendial
    - Analytical procedures and acceptance criteria – brief description of manufacture and controls or an authorized reference to a DMF or NDA for Phase 2
    - Full description of the characterization, manufacture, control, analytical procedures, and acceptance criteria for Phase 3
- Manufacturer
  - Any changes during earlier phase(s) including contractor

Drug Product for Phases 2 & 3 (cont'd)

- Method of manufacturing, packaging and process controls
  - A brief general step by step description for the unit dose
  - Flow diagram
  - Information on specific equipment, packaging and labeling process, in-process controls except for sterile products or atypical dosage forms not needed for Phase 2. Information on key equipment employed is needed for Phase 3
  - Reprocessing procedures and controls - safety related information for Phase 2 and description for Phase 3
  - Brief description of the packaging and labeling for clinical supplies for Phase 3
  - Sterile products
    - Changes in the drug product sterilization process
    - Other changes in the process to sterilize bulk drug substance or drug product, components, packaging, and related items
    - Validation of the sterilization process is not needed

Drug Product for Phases 2 & 3 (cont'd)

- Specification
  - Changes to specifications (tests and acceptance criteria)
  - Data updates on the degradation profile
  - Identification & qualification of degradation products for Phase 3
  - Summary table of the test results, analytical data, and COA for the lots used in clinical studies
- Container closure system
  - Updates on information previously filed
  - The container closure system of certain drug products delivered by devices (e.g., MDIs, DPIs) should be similar to that intended for the marketed product
  - Name of the manufacturer and supplier
  - DMF reference and authorization, if available
  - Additional information may be recommended for atypical delivery systems (e.g., MDIs, disposable injection devices)

Drug Product for Phases 2 & 3 (cont'd)

- Stability
  - Stability protocol (detailed protocol for Phase 3)
  - Preliminary stability data based on representative material for Phase 2 and detailed stability data for Phase 3
  - All available stability data for the clinical material used in earlier phase(s)
  - Stress testing results for Phase 3
  - Container closure integrity tests for sterile products, where applicable - discussion for Phase 3

CMC Submission Differences between INDs and NDAs

- ICH Quality Guidelines
  - Do not apply to INDs submissions
- Pharmaceutical Development Information
  - Not needed for all phases of IND
- DS Characterization
  - Some data to support the proposed structure in early IND Phases versus full characterization for NDA
- Specifications for Drug Substance and Drug Product
  - Tentative acceptance criteria (e.g., safety levels of solvents) from a few small IND batches, vs. those based on multiple pilot- or full-scale batches, and statistical analysis for NDA
- Validation of Analytical Procedures
  - Scientifically sound analytical procedures without full validation, vs. full validation for NDA

CMC Submission Differences between INDs and NDAs (cont.)

- Impurities
  - Identification vs. identification & qualification for NDA
- Process Validation
  - Not required for INDs
  - Can be completed after NDA approval
- Stability Protocols
  - Detailed protocol not needed for Phase 1
- Stability Data and Shelf Life
  - Data to support the duration of clinical studies during IND phase vs. to support the shelf life for NDA

FDA Meetings with IND Sponsors or NDA Applicants

- Pre-IND meetings/consultations
  - Help sponsors, unfamiliar with the IND process or with questions not fully answered by FDA guidances/MaPPs, plan a drug development program or prepare an IND submission
- End-of-Phase 2 meetings
  - Ensure that meaningful and adequate data are generated during Phase 3 studies
  - Discuss and agree on plans/protocols
  - 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
- 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

CGMP for Phase 1 IND

- CGMP regulation, 21 CFR 211, revised in July 08
  - Exempts a drug for Phase 1 study from CGMP requirements, unless the drug has been made available in a Phase 2 or 3 study or has been lawfully marketed
- CGMP Guidance for Phase 1 INDs, issued July 08
  - Recognizes that some manufacturing controls and the extent of controls do differ between investigational and commercial manufacture and among various phases of clinical studies
  - Recommends appropriate QC procedures to ensure quality and safety of study drug
  - FDA continues to exercise oversight of the study drug under general CGMP authority and through review of IND

Summary

- FDA drug laws and regulations have evolved over time
- IND is an exception to the NDA/ANDA under the law
- IND regulatory oversight
  - It is a phased approach
  - It focuses on safety as primary review objective for Phase 1
  - Amount of CMC and pharm/tox depends on phase of IND, duration of study, dosage form, etc.
  - Sponsor consultation with FDA (e.g., pre-IND, EOP2) is key to mutually accepted trial designs, higher quality IND and NDA submissions, and more efficient review