Dr. Zahra Shahrokh

- Zahra Shahrokh has 25 years experience in developing biotechnology products, with track record of global regulatory approvals of 5 recombinant proteins and clinical development of dozens of therapeutics. She is currently Chief Development Officer at STC Biologics and a CMC Consultant. Prior to that she was at Shire for ten years as Head of Pharmaceutical and Analytical Development and also as Head of CMC Program Management, where she built organizational capability from a start-up towards a multi-billion dollar commercial organization. Prior to that, she had technical and leadership roles at Genentech's Pharmaceutical R&D department for ten years.

- Zahra has a PhD in Biophysics from UC, Berkeley, dual BA in Chemistry and Physics from University of Pennsylvania, Philadelphia, and holds several patents and over 60 papers & invited presentations. She is an active Organizing Committee member for WCBP's "CMC Strategy Forum" that brings together regulators and biotech industry to present and debate current topics in product development.

What's in an IND? Guide to Writing IND For Biologics

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NIH/NINDS

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The views expressed in this presentation are the views of the presenter and do not necessarily represent the views of the NIH

Presentation Outline

- Some Definitions
- BLA vs NDA
- Product Development Phases and Regulatory Interactions
- Regulatory Filing Formats and Review Process
  - IND and its types
  - CTA/IMPD (US vs EU)
  - CTD format (global)
- What's in an IND?
  - Crafting the IND -the questions Regulators ask
  - Purpose of each section and their links
- Examples of gaps and deficiencies

Some Definitions

Regulatory Application Terms:

- IND Application = Investigational New Drug Application (FDA term)
- CTA = Clinical Trial Application (EU term)
- BLA / NDA (FDA terms) = Biological License Application (for Biologics) / New Drug Application (for small molecules)
- MAA (EU term) = Marketing Authorization Application
- CTD = Common Technical Document (format for global submission)

Quality Terms:

- CMC = Chemistry, Manufacturing, and Controls
- DS = Drug Substance (Biologics), API (small molecules): purified active substance that is intended to provide pharmacological/medicinal activity
- DP = Drug Product: the finished dosage form that contains the drug substance and often other excipients

Clinical Terms:

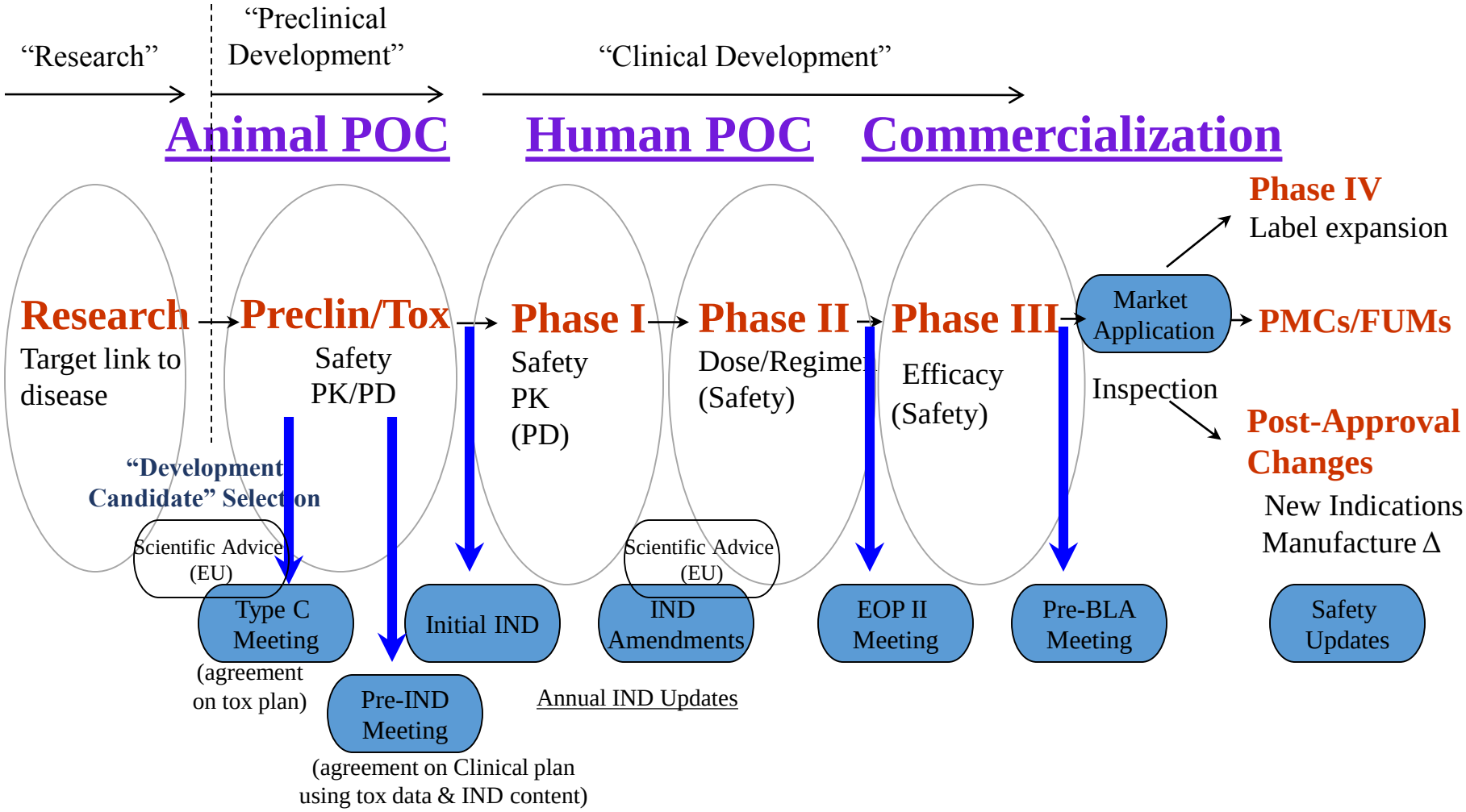
- CRF = Case Report Form
- IB = Investigator's Brochure
- IRB/IEC = Institutional Review Board/Independent Ethics Committee

What Modalities Are Filed as a BLA rather than an NDA?

- BLA
  - Virus, therapeutic serum, toxins, antitoxins, or blood related products
  - Therapeutic proteins (recombinant)
  - Diagnostic devices
  - Gene therapy
  - Human tissues, cellular products
  - Vaccines, Xenotransplantation products
- NDA
  - Small molecules (synthetic compounds)

This talk focuses on IND sections for <u>therapeutic proteins</u>

Product Development Phases & Regulatory Authority Interactions



IND = Investigational New Drug Application; BLA=Biologics License Application
PMC = Post-marketing commitments to the FDA; FUM = Follow-up-Measures for EMA

Moving Through Clinical Trials To and Beyond Commercialization

- **Phase I trials**, sometimes called first-in-human trials, test a small number of subjects to find out how the treatment works in the body.
  - find the lowest dose at which the treatment is effective (the minimum therapeutic dose) and the highest dose at which it can be taken without causing harm
  - **Assure safety and rights of subjects**
  - **May be done in healthy volunteers or in patients (e.g. orphan drugs, neurological indications)**
- **Phase II trials** test the treatment in several hundred patients with a given disease or condition.
  - find out how well the treatment works in larger numbers, identify common side effects, and refine the dose and length of treatment.
- **Phase III trials** typically compare the treatment across several thousand patients
  - to gather more detailed information on how well it works in groups of patients and its safety.
  - the results influence the prescribing and patient information of a medicine once it is marketed.
- **Phase IV trials** are carried out after a medicine has been licensed and put on the market.
  - find out more about the long term harms and benefits of a medicine and to discover new uses for it.

Filing in US vs Europe

US	Europe
one agency –FDA (reviewers within the same agency)	Multiple agencies • European Medicines Agency (EMA) – administrative organization • Committee for Medicinal Products for Human Use (CHMP) of the EMA – scientific input • National Health Agencies (differences in culture and medical practices)
Bottom up	Top down
More specific	Benefit/Risk of entire data
Same data package to both, probably not the same outcome	

US IND vs CTA in EU

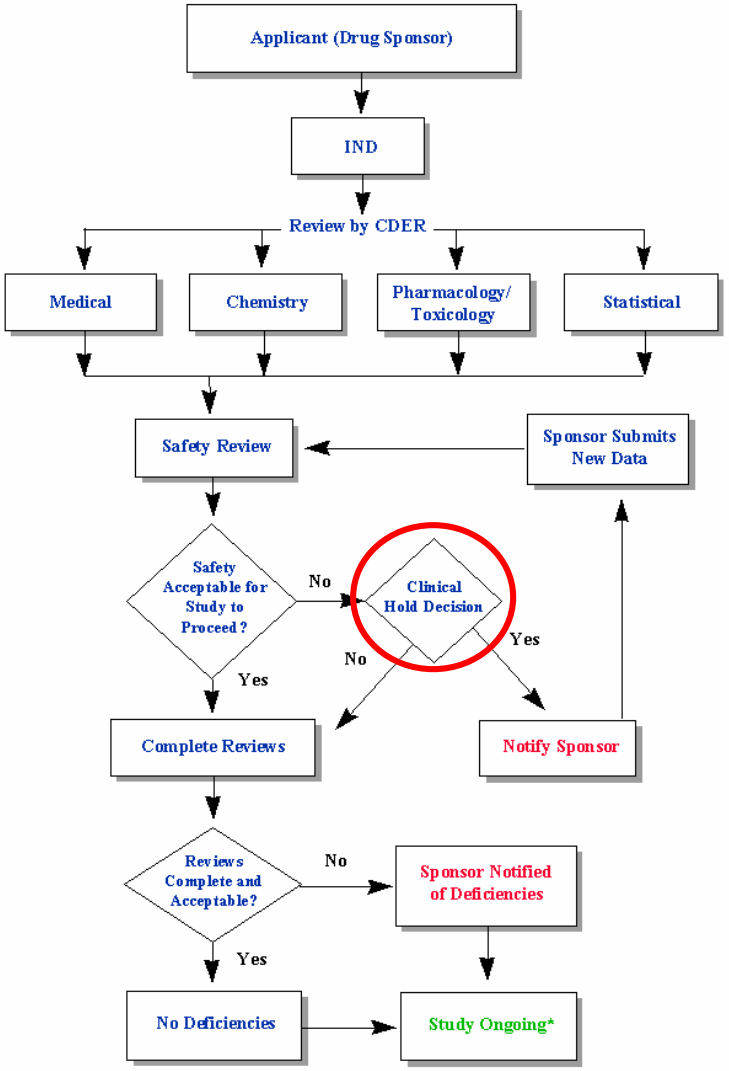
IND (Investigational New Drug Application)	CTA (Clinical Trial Application)
Form FDA 1571 Table of Contents Introductory Statement General investigational plan Investigator's brochure Protocol: Study protocol Investigator data Facilities data IRB data CMC data Pharm and Tox data Previous Human Experience Additional Information	Application form (12 pg form) Cover letter Investigational brochure Protocol: Study protocol Investigator data (some MS) Facilities data (some MS) EC data (copy of opinion) IMPD: Quality data Pharm and Tox data Previous Human Experience Risk and benefit assessment

IRB = Institutional Review Board; IMPD = Investigational Medicinal Product Dossier

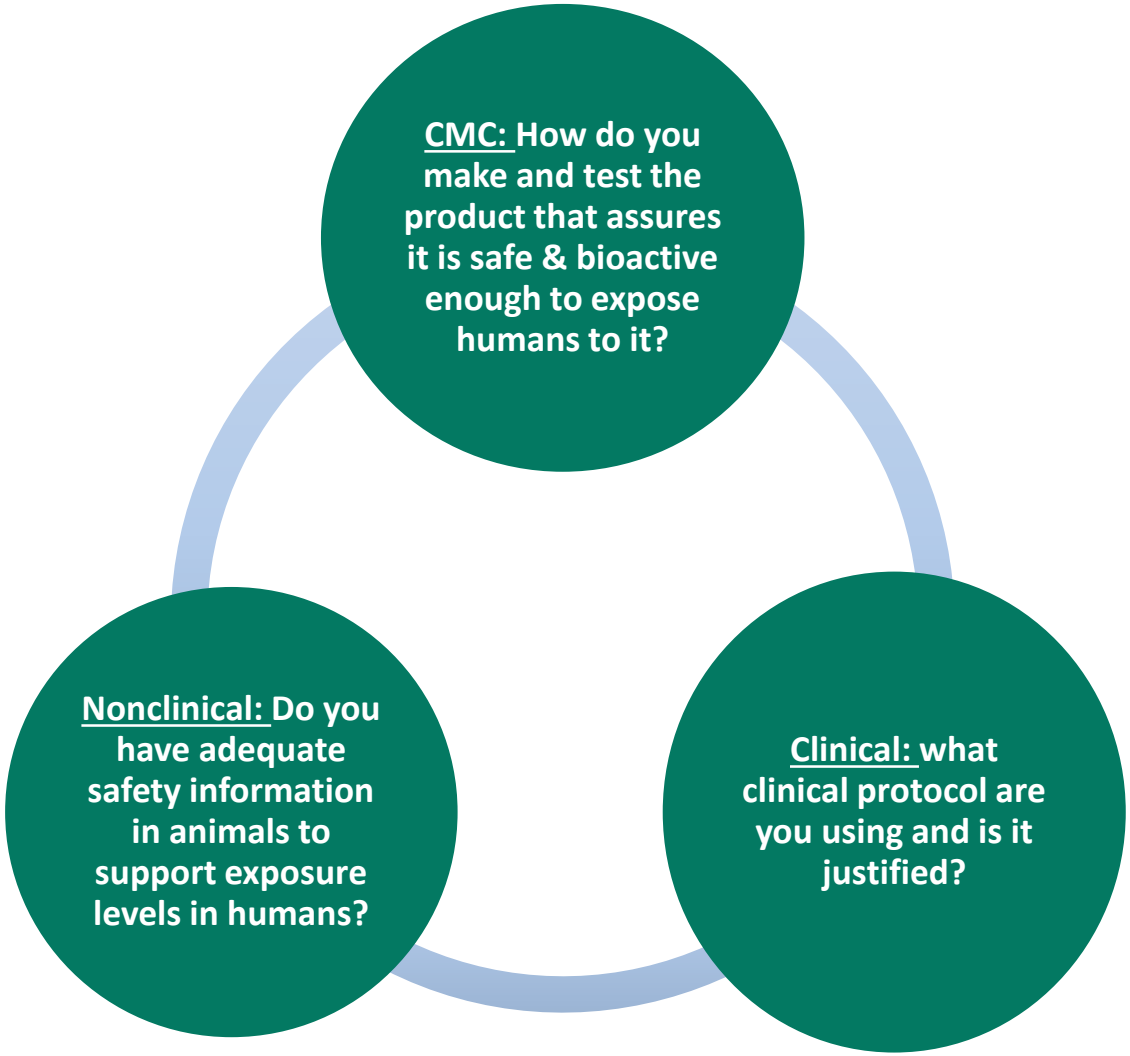
File Review Process

- For US INDs –wait 30 days from official FDA receipt of IND (effective date); if no comments proceed with dosing patients -→ see schematic to the right

- For EU –in 30 days comments will be provided of any deficiencies; must wait for both Ethics Committee and National Competent Authority approval before proceeding (120 days)



What's in an IND?



Crafting the IND/CTA Application

- Your submission for First in Human (FIH) trial should provide the reviewers with the assurance that:
  a. the study will not expose the subjects to unjustified risk
  b. the subjects may potentially benefit from the use of the product (*with the exception of healthy volunteer studies where the subjects would not necessarily experience a clinical benefit from the drug*)
- CMC: Show that you have a defined way of producing and testing the drug, that you have appropriate materials and process controls in place for ensuring the product will have appropriate purity, activity, stability, and accuracy of dosage for human use.
- Nonclinical: Show that you have adequate preclinical safety data to minimize risk to patients and that the toxicology data provides appropriate coverage/safety margin for dosing humans
- Clinical: Show that the clinical protocol will use appropriate subjects (inclusion/exclusion criteria), appropriate safety measures and risk mitigation (tests, study monitors, data integrity, CRFs), and that the subject rights are honored (informed consent)

Be succinct (this is not a technical report), be accurate (credibility), tell a story

Organizing for IND Writing

- Start preparing ~9 months ahead of target submission date
  - Define internal and external partners/consultants/CROs
  - Set up systems, read regulatory guidance documents
- Before writing (~4 months), get all functional areas together and discuss:
  - what information each function has/should have
  - what information do they need from another group
  - who is the main responsible author and who are all supporting authors
  - who will review each section, **who will review all sections for consistency across sections**
  - Watch out for different styles of different authors

- ***Annual Updates and IND amendments*** *for later stage clinical trials should show:*
  - *Increased product knowledge, more stability data*
  - *Improved manufacturing process (purity/activity or process consistency)*
  - *Tighter specifications*
  - *Update to nonclinical and clinical studies*

What's in an IND: Common Technical Document (CTD) Format

A harmonized format of submissions used across ICH countries (EU, Japan, US) and accepted in major other regions

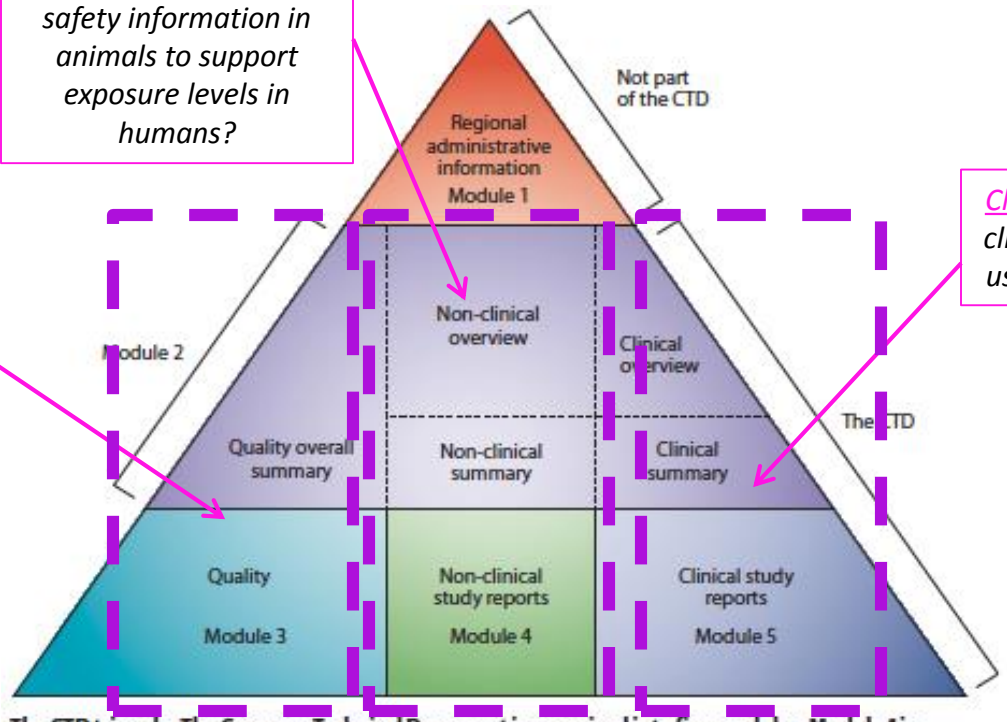
http://www.ich.org/products/ctd.html

Electronic CTD (eCTD)

Nonclinical Module 4: *Do you have adequate safety information in animals to support exposure levels in humans?*

CMC Module 3: *How do you make and test the product that assures it is safe & bioactive enough to expose humans to it?*

Clinical Module 5: *what clinical protocol are you using and is it justified?*



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

IND Content

- Cover Sheet
- Table of Contents
- Introductory Statement and General Investigational Plan
- Investigator's Brochure
- Protocols
- CMC Section
- Pharmacology and Toxicology Information
- Previous Human Experience

CTD or eCTD format

- Table of Contents
- Module 1: Administrative Information
  - Forms, Cover letter, Contacts, Financial/Legal certifications, Agency Meetings, Annual Reports, Labeling, Investigator's Brochure (**General investigation plan for initial IND**)
- Module 2: Summaries (*usually not in Phase I*)
- Module 3: Quality (CMC)
- Module 4: Nonclinical Study Reports
- Module 5: Clinical Study Reports

Guidance for Industry. Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products . *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074980.pdf*

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073257.pdf

IND Introductory Statement and General Investigational Plan

- Purpose:
  - To place the developmental plan into perspective and to help FDA anticipate sponsor needs.
- Typical plan for Phase I:
  - close monitoring of human subjects for dose-dependent safety
  - determine early pharmacokinetic, perhaps early pharmacodynamic and pharmacological properties of the drug
  - Sometimes use drug as a research tool to explore biological phenomena or disease processes
- Be brief: 2-3 pages (it is expected for plans to change during later phases)

Understanding CMC Sub-Sections (Module 3) and Their Links

3.2.S Drug Substance

3.2.P Drug Product

Common elements in the two sections:

- Manufacturer, testing sites, stability sites
- Manufacturing process descriptions and in-process controls
- Control of raw materials and drug itself (specs, assays)
- Batch analyses
- Stability data and summary assessment

Unique elements:

- Elucidation of structure (product and impurity characterization details, forced degradation studies) in DS
- Formulation development in DP
- Compatability and in-use studies in DP

Manufacturing Process

Characterization Section

- Primary structure (peptide map/MS, etc)
- Secondary and tertiary structures (CD, etc)
- Other biophysical characterization (DSC)
- Molecular weight and size distribution (MS, SEC, SDS-PAGE)
- Charge Variants (HPLC, CE)
- Glycosylation
- Biological activity
- (Forced degradation studies)
- *[Critical Quality Attributes (CQAs)]*

Impurities (and their control)

- Process related (host cell DNA, host cell proteins, column leachates, etc)
- Product related (aggregates, fragments, other degradation products)

For DP: show how the process of going from DS to DP manufacture affects impurities or degradation products

Manufacturer (sites of production, testing, stability programs, labeling, storage) *DS & DP*

Description of Manufacturing Process and Process Controls

(Process flow, in-process tests, critical steps and their control) *DS & DP*

Manufacturing Process Development

For DS:

- Cell line development
- Cell culture process and recovery Purification process development, DS fill, storage
- Process changes and comparability

For DP:

- DS thaw & pool, and aseptic processing
- Lyophilization cycle development (if applicable)

Characterization, Analytics, Specifications

Characterization Section

- Primary structure (peptide map/MS, etc)
- Secondary and tertiary structures (CD, etc)
- Other biophysical characterization (DSC)
- Molecular weight and size distribution (MS, SEC, SDS-PAGE)
- Charge Variants (HPLC, CE)
- Glycosylation
- Biological activity
- (Forced degradation studies)
- *[Critical Quality Attributes (CQAs)]*

Impurities (and their control) (DS and DP)

- Process related (host cell DNA, host cell proteins, column leachates, etc.)
- Product related (aggregates, fragments, other degradation products)

Analytical Procedures

(DS and DP)

Release tests (*a subset of characterization assays, tied to CQAs*)

Stability tests

Specifications (i.e. Release Tests and Acceptance Criteria) (DS and DP)

Justification of Specifications (DS and DP) (based on analytical and manufacturing capabilities, stability)

Batch Analysis (DS and DP)

Stability Data (DS and DP)

Formulation, Stability

Formulation Development (Preformulation studies showing biophysical and biochemical understanding of product stability

- Rationalize selected protein conc, pH, buffer, excipients, etc

Forced Degradation Studies

- What are the product susceptibilities (heat, pH, light, oxidants, etc)
- What are the stability indicating assays

Characterization (how well you understand degradation products, what are their levels, are they active? what is known of their safety?

Container-Closure System

Leachables/Extractables (e.g. do leachables impact stability)

Manufacturing Process Description (e.g. if lyophilized, how does that impact product quality/stability)

Stability Summary and Conclusions

- What batches, what conditions
- Stability schedule
- Stability assays and specs
- How much data available on how many batches
- What is the data saying
- Propose and justify shelf life

Compatability, In-Use Studies

(stability of dose preparations, in IV bag)

Module 4: Nonclinical Section

General Considerations:

- Conduct pharmacokinetic and toxicity studies using the same schedule, duration, formulation, and route as proposed clinical trial
- *Results must be sufficient to determine the starting dose for clinical studies*

IND Sections:

- Pharmacology Reports
  - Mechanism of Action; Cross-Reactivity of drug with normal human tissue and with limited tissue from X, Y animal species; Safety Pharmacology
- PK Reports
  - Bioanalytical Methods, Drug Interaction, PK in species X, Y
- Toxicology Reports
  - Single dose acute tox studies: usually in 2 species: a) general, life-threatening toxicity study in rodents; b) study in a relevant species that confirms dose tolerability (usually primates for biologics because of tissue cross reactivity).
  - Repeat dose tox studies
  - Genotoxicity (usually not for biologics), Carcinogenicity (usually not for biologics), Reproductive & Developmental Toxicity (usually by Phase 3)
- Local tolerance (for other delivery routes than IV)
- Immunogenicity

Module 5: Clinical Section

- 5.2 Tabular listing of all clinical studies
- 5.3 Clinical Study Reports
  - Reports of Biopharmaceutical Studies
  - Reports of Studies Pertinent to Human PK
  - Reports of Human PK Studies
  - Reports of Human PD Studies
  - Reports of Efficacy and Safety Studies
  - *Reports of post-marketing experience (not for IND)*
  - *CRFs*
  - *Literature References*

Links Between Nonclinical and Clinical Sub-Sections

Nonclinical Pharmacology
Mechanism of Action
Cross reactivity of drug to animal tissues
Cross reactivity of drug to human tissues

Nonclinical PK to rationalize dose, regimen

Clinical PK (and supporting studies such as plasma binding, shed antigens, metabolism)

Nonclinical Efficacy/PD

Nonclinical Toxicology
Rationale for tox species
Tox studies to support human starting dose, max dose, frequency of dosing

Clinical Safety

Clinical PD

Clinical Efficacy

Examples of Deficiencies and Mis-Steps Towards IND

1. Tox studies not adequately covering clinical dosing regimen
   - *Meet with FDA before conducting tox studies, present plan and justify it (Look up "FDA Type C Meeting" on www.fda.gov)*
2. Missing antidrug antibody assays or not validating bioanalytical assays
   - *Bioanalytical assays (PK and ADA) have to be developed for all biologics for Phase I and validated for clinical studies*
     - *"FDA Draft Guidance on Assay Development for Immunogenicity Testing of Therapeutic Proteins"*
   - *Poor assays for detecting residual host cell proteins have made a company go bankrupt at the finish line!!*
     - *Great article explaining ADA assays: Shankar et al. "Recommendations for the Validation of Immunoassays used for Detection of Host Antibodies Against Biotechnology Products" J. Pharm. Biomedical Analysis, 2008.*

Example: “R” to “D” Transition Deficiency

- “R” had identified promising anticancer cytokine
- Several variants in late stage research; but “development candidate” selection was challenging
  - Variable/inconsistent animal model efficacy results
- “D” started collaborating
  - Purified proteins were kept refrigerated until dosing (stability not known)
  - Animals dosed via Alzet minipump delivery system (drug at 37°C in PBS for 20 days)
- pH-temperature stability studies showed aggregation at 37°C in PBS (pH 7.2); pH 5 optimal
- New formulation provided consistent animal study results
- Additional structure and stability studies of variants also helped identify optimal development candidate
- Project moved into IND-enabling development stage

Example ctd…: IND-enabling development stage

- Primate tox studies showed severe nephrotoxicity; program dropped
- Previous biophysical studies in “D” had shown human cytokine trimerizes human receptors (required for bioactivity), but only dimerizes monkey receptors
- “R” studies showed that dimerized receptor by monkey cytokine results in cellular toxicity (not seen with human cytokine)
  - Single amino acid difference between human and monkey cytokine impacted receptor oligomerization state and subsequent toxicity profile
- Monkey cytokine was made and used for repeating monkey tox studies
  - Clean tox studies observed --> program was revived and proceeded to clinical development

Formulation and analytical/biophysical characterization have been key missed aspects of many preclinical studies

More on Formulation Mis-steps

- "Drug in PBS" common in research is often not a good long term formulation for proteins
  - Proteins often aggregate if you freeze them in PBS due to precipitation of the dibasic phosphate and drop in pH by 3-4 units
  - Do you have a suitable size exclusion HPLC assay to monitor soluble aggregates? Did you do a multi-cycle freeze-thaw study on your drug formulation and test by HPLC?
- "Particulates when protein is diluted in IV bag" is often missed until in the clinic
  - Proteins tend to form visible and subvisible particles of immunogenicity concern
  - Appearance by the eye is a key assay that can tell there is instability; other methods of light obscuration by Hiac and microfluid imaging MFI measure subvisible particles should be used as part of formulation development studies

Preformulation and formulation development studies are essential in early development to ensure drug stability over long term and during shipping, accidental freezing and other temperature excursions

Example: Uninformed Development "go" decision

- Enzyme showed great efficacy in animal models
- Program moved to IND-enabling process development stage
- Molecule made in PD did not show animal efficacy and had significant solubility issues
- Investigation indicated that previous efficacy studies were done with mouse enzyme, while PD was developing human enzyme
- Human enzyme had significantly different physicochemical properties (different charge variants and glycosylation) than mouse enzyme
- Human enzyme did not have the same binding affinity to mouse cells *in vitro*
- 1.5 years and $1.5 mil spent, program dropped

Poor basis of Development "go decision" with no understanding of structure-function

Avoid Development Mis-Steps That Delay Program Before, At, and After IND

- Remove “R” & “D” disconnect –bring a team of experts in CMC, preclinical, and clinical and **INTEGRATE THEM**!
- Develop good analytics to assess product quality and stability
- Pay attention to formulation
- Watch out for quick and “dirty” Phase I development –could come back and delay program significantly

Additional Details & References

CMC Sections (Module 3) –"S" Drug Substance

IMPD Numbering System

- 2.1.S **DRUG SUBSTANCE**
- 2.1.S.1 General Information
  - 2.1.S.1.1 Nomenclature
  - 2.1.S.1.2 Structure
  - 2.1.S.1.3 General Properties
- 2.1.S.2 Manufacture
  - 2.1.S.2.1 Manufacturer(s)
  - 2.1.S.2.2 Description of Manufacturing Process and Process Controls
  - 2.1.S.2.3 Control of Materials
  - 2.1.S.2.4 Control of Critical Steps and Intermediates
  - 2.2.1.S.2.5 Process Validation and/or Evaluation
  - 2.2.1.S.2.6. Manufacturing Process Development
- 2.1.2.S.3 Characterization
  - 2.1.2.S.3.1 Elucidation of Structure and other Characteristics
  - 2.1.2.S.3.2 Impurities
- 2.2.1.S.4 Control of the Drug Substance
  - 2.2.1.S.4.1 Specification(s)
  - 2.2.1.S.4.2 Analytical Procedures
  - 2.2.1.S.4.3 Validation of Analytical Procedures
  - 2.2.1.S.4.4 Batch Analyses
  - 2.2.1.S.4.5 Justification of Specification(s)
- 2.2.1.S.5 Reference Standards or Materials
- 2.2.1.S.6 Container Closure System
- 2.2.1.S.7 Stability
  - 2.2.1.S.7.1 Stability Summary and Conclusions
  - 2.2.1.S.7.2 Post-Marketing Stability Commitments
  - 2.2.1.S.7.3 Stability Data

IND/CTD Numbering System

- 3.2.S **DRUG SUBSTANCE**
- 3.2.S.1 General Information
  - 3.2.S.1.1 Nomenclature
  - 3.2.S.1.2 Structure
  - 3.2.S.1.3 General Properties
- 3.2.S.2 Manufacture
  - 3.2.S.2.1 Manufacturer(s)
  - 3.2.S.2.2 Description of Manufacturing Process and Process Controls
  - 3.2.S.2.3 Control of Materials
  - 3.2.S.2.4 Control of Critical Steps and Intermediates
  - 3.2.S.2.5 Process Validation and/or Evaluation
  - 3.2.S.2.6. Manufacturing Process Development
- 3.2.S.3 Characterization
  - 3.2.S.3.1 Elucidation of Structure and other Characteristics
  - 3.2.S.3.2 Impurities
- 3.2.S.4 Control of the Drug Substance
  - 3.2.S.4.1 Specification(s)
  - 3.2.S.4.2 Analytical Procedures
  - 3.2.S.4.3 Validation of Analytical Procedures
  - 3.2.S.4.4 Batch Analyses
  - 3.2.S.4.5 Justification of Specification(s)
- 3.2.S.5 Reference Standards or Materials
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability
  - 3.2.S.7.1 Stability Summary and Conclusions
  - 3.2.S.7.2 Post-Marketing Stability Commitments
  - 3.2.S.7.3 Stability Data

CMC Sections (Module 3) –"P" Drug Product

IMPD Numbering System

- 2.1.P **MEDICINAL Product**
- 2.1.P.1 Description and Composition of Drug Product
- 2.1.P.2 Pharmaceutical Development
  - 2.1.P.2.1 Components of Drug Product
  - 2.1.P.2.2 Drug Product
    - 2.1.P.2.2.1 Formulation Development
    - 2.1.P.2.2.2 Overages
    - 2.1.P.2.2.3 Physicochemical Properties
  - 2.1.P.2.3 Manufacturing Process Development
  - 2.1.P.2.4 Container Closure System
  - 2.1.P.2.5 Microbiological Attributes
  - 2.1.P.2.5 Comparability (in-use studies)
- 2.1.P.3 Manufacture
  - 2.1.P.3.1 Manufacturer(s)
  - 2.1.P.3.2 Batch Formula
  - 2.1.P.3.3 Description of Manufacturing Process and Process Controls
  - 2.1.P.3.4 Control of Critical Steps and Intermediates
  - 2.1.P.3.5 Process Validation and/or Evaluation
  - 2.1.P.2.6 Manufacturing Process Development
- 2.1.P.4 Control of Excipients
  - 2.1.P.4.1 Specifications
  - 2.1.P.4.2 Analytical Procedures
  - 2.1.P.4.3 Validation of Analytical Procedures
  - 2.1.P.4.4 Justification of Specifications
  - 2.1.P.4.5 Excipients of Human or Animal Origin
  - 2.1.P.4.6 Novel Excipients

IND Numbering System

- 3.2.P **DRUG Product**
- 3.2.P.1 Description and Composition of Drug Product
- 3.2.P.2 Pharmaceutical Development
  - 3.2.P.2.1 Components of Drug Product
  - 3.2.P.2.2 Drug Product
    - 3.2.P.2.2.1 Formulation Development
    - 3.2.P.2.2.2 Overages
    - 3.2.P.2.2.3 Physicochemical Properties
  - 3.2.P.2.3 Manufacturing Process Development
  - 3.2.P.2.4 Container Closure System
  - 3.2.P.2.5 Microbiological Attributes
  - 3.2.P.2.5 Comparability (in-use studies)
- 3.2.P.3 Manufacture
  - 3.2.P.3.1 Manufacturer(s)
  - 3.2.P.3.2 Batch Formula
  - 3.2.P.3.3 Description of Manufacturing Process and Process Controls
  - 3.2.P.3.4 Control of Critical Steps and Intermediates
  - 3.2.P.3.5 Process Validation and/or Evaluation
  - 3.2.P.2.6 Manufacturing Process Development
- 3.2.P.4 Control of Excipients
  - 3.2.P.4.1 Specifications
  - 3.2.P.4.2 Analytical Procedures
  - 3.2.P.4.3 Validation of Analytical Procedures
  - 3.2.P.4.4 Justification of Specifications
  - 3.2.P.4.5 Excipients of Human or Animal Origin
  - 3.2.P.4.6 Novel Excipients

CMC Sections (Module 3) –"P" Drug Product ctd…

IMPD Numbering System

- 2.1.P.5 Control of Drug Product
  - 2.1.P.5.1 Specification(s)
  - 2.1.P.5.2 Analytical Procedures
  - 2.1.P.5.3 Validation of Analytical Procedures
  - 2.1.P.5.4 Batch Analyses
  - 2.1.P.5.5 Characterization of Impurities
  - 2.1.P.5.6 Justification of Specification(s)
- 2.1.P.6 Reference Standards or Materials
- 2.1.P.7 Container Closure System
- 2.1.P.8 Stability
  - 2.1.P.81 Stability Summary and Conclusions
  - 2.1.P.8.2 Post-Marketing Stability Commitments
  - 2.1.P.8.3 Stability Data

IND Numbering System

- 3.2.P.5 Control of Drug Product
  - 3.2.P.5.1 Specification(s)
  - 3.2.P.5.2 Analytical Procedures
  - 3.2.P.5.3 Validation of Analytical Procedures
  - 3.2.P.5.4 Batch Analyses
  - 3.2.P.5.5 Characterization of Impurities
  - 3.2.P.5.6 Justification of Specification(s)
- 3.2.P.6 Reference Standards or Materials
- 3.2.P.7 Container Closure System
- 3.2.P.8 Stability
  - 3.2.P.81 Stability Summary and Conclusions
  - 3.2.P.8.2 Post-Marketing Stability Commitments
  - 3.2.P.8.3 Stability Data

CMC Sections (Module 3) –Appendices

IMPD Numbering System

- 2.A Appendices
  - 2.A.1 Facilities and Equipment
  - 2.A.2 Adventitious Agents Safety Evaluation
  - 2.A.2.1 Non-viral Adventitious Agents
  - 2.A.2.2 Viral Adventitious Agents
- 2.A.3 Novel Excipients

IND Numbering System

- 3.2.A Appendices
  - 3.2.A.1 Facilities and Equipment
  - 3.2.A.2 Adventitious Agents Safety Evaluation
  - 3.2.A.2.1 Non-viral Adventitious Agents
  - 3.2.A.2.2 Viral Adventitious Agents
- 3.2.A.3 Novel Excipients
- 3.2.R Regional Information
  - 3.2.R.1 Executed Batch Records
  - 3.2.R.2 Method Validation Package
  - 3.2.R.3 Comparability Protocols
- 3.3 Key Literature References

Nonclinical Sections (Module 4)

IND/CTD Numbering System

- 4.1 TOC
- 4.2 Study Reports
- 4.2.1 Pharmacology
  - 4.2.1.1 Primary Pharmacodynamics
  - 4.2.1.2 Secondary Pharmacodynamics
  - 4.2.1.3 Safety Pharmacology
  - 4.2.1.4 Pharmacodynamic Drug Interaction
- 4.2.2 Pharmacokinetics
  - 4.2.2.1 Analytical Methods and Validation Reports
  - 4.2.2.2 Absorption
  - 4.2.2.3 Distribution
  - 4.2.2.4 Metabolism
  - 4.2.2.5 Excretion
  - 4.2.2.6 Pharmacokinetic Drug Interactions
  - 4.2.2.7 Other Pharmacokinetic Studies

IND/CTD Numbering System

- 4.2.3 Toxicology
  - 4.2.3.1 Single-Dose Toxicity
  - 4.2.3.2 Repeat-Dose Toxicity
  - 4.2.3.3 Genotoxicity
    - In vitro studies
    - In vivo studies
  - 4.2.3.4 Carcinogenicity
  - 4.2.3.5 Reproductive and Development Toxicity
    - Fertility and Embryonic Development
    - Embryo-Fetal Development
    - Pre- and Post-natal Development & Maternal Function
    - Offspring, Juvenile, Second & Third-Generation Studies
  - 4.2.3.6 Local Tolerance
  - 4.2.3.7 Other Toxicity Studies
    - Antigenicity
    - Immunogenicity
    - Mechanistic Studies (not included elsewhere)
    - Dependence
    - Metabolites
    - Impurities
- 4.3 Literature References

Clinical Sections (Module 5)

IND/CTD Numbering System

- 5.1 TOC
- 5.2 Tabular listing of all clinical studies
  - 5.2.1 “CLIENT” Studies
  - 5.2.2 Tabular listing of clinical investigations
- 5.3 Clinical Study Reports
  - 5.3.1 Reports of Biopharmaceutic Studies
    - 5.3.1.1 Bioavailability study reports
      - “CLIENT” studies
        - Protocol ###
        - Protocol ###
      - Reference Listed Drug Sponsor Studies
      - Published studies
      - Summary
    - 5.3.1.2 Comparative BA and BE Study Reports
      - “CLIENT” studies *(repeat for each protocol; same for Drug Sponsor Studies)*
        - Protocol **####**
        - Appendices 16.0
        - Appendices 16.1 – Study Information
        - Appendices 16.1.1 – Protocol & IRB Approval
        - Appendices 16.1.2 – Sample Case Report Form (CRF)
        - Appendices 16.1.3 – IRB Membership
        - Appendices 16.1.5 – Signature Page
        - Appendices 16.1.6 – Table of Dosing Dates and Times
        - Appendices 16.1.7 – Randomization Scheme and Codes
        - Appendices 16.1.8 – Audit Certificate
        - Appendices 16.1.9 – Statistical Report
    - 5.3.1.3 *In vitro/In vivo* Correlation (IV/IVC)
    - 5.3.1.4 Bioanalytical and Analytical Methodsx

Clinical Section (Module 5) ctd…

IND/CTD Numbering System

- 5.3.2 Reports of Studies Pertinent to Human PK
  - 5.3.2.1 Plasma protein binding study report
  - 5.3.2.2 Hepatic metabolism/drug interactions
  - 5.3.2.3 Studies using other human materials
- 5.3.3 Reports of Human PK Studies
  - 5.3.3.1 Healthy subject PK and tolerability
  - 5.3.2 Patient PK and initial tolerability
  - 5.3.3 Intrinsic factor PK
  - 5.3.4 Extrinsic factor PK
  - 5.3.5 Population PK
- 5.3.4 Reports of Human PD Studies
  - 5.3.4.1 Healthy subject PD and PK/PD studies
  - 5.3.4.2 Patient PD and PK/PD studies
- 5.3.5 Reports of Efficacy and Safety Studies
  - 5.3.5.1A Indication #1
  - 5.3.5.1B Indication #2
  - 5.3.5.2 Uncontrolled Clinical Studies
    - "CLIENT" Studies
    - NDA **##,###** Sponsor Studies
      - Summary Basis of Approval: Clinical Review
    - Published Studies
    - Summary
  - 5.3.5.3 Reports of Analyses of Data from More than One Study
    - Integrated Summary of Safety
    - Integrated Summary of Efficacy
  - 5.3.5.4 Other Clinical Study Reports
- 5.3.6 Reports of Post-Marketing Experience

5.4 Literature References

Guidelines for INDs and The Law

1. FDA website: www.fda.gov
2. European Medicinal Agency (EMA) website: http://www.ema.europa.eu/ema/
3. The IND webpage: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm
4. Procedures for Drug Approval in Different Countries: http://www.jddtonline.info/index.php/jddt/article/viewFile/409/276
5. CTD website: http://www.ich.org/products/ctd.html
6. FDA site describing road map to IND: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm
7. EMA IMPD guidance: http://www.imp-dossier.eu/imdp_guidance/
8. Take a Quiz with FDA! http://www.accessdata.fda.gov/cder/cmc/topic10/topic10/da_01_10_0030.htm

US Code of Federal Regulations Related to Drugs

Of the 1402 CFRs, about a dozen are related to drugs:

- 21 CFR Part 11_Electronic records; electronic signatures.
- 21 CFR 50_Protection of human subjects and informed consent regulations
- 21 CFR Part 54_Financial disclosure by clinical investigators
- 21 CFR Part 56_IRB regulations
- 21 CFR Part 58_GLP regulations for nonclinical studies
- 21 CFR Part 201_Drug labeling
- 21 CFR Part 210_Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs: General.
- 21 CFR Part 211_Current good manufacturing practice for finished pharmaceuticals.
- 21 CFR 312_IND regulations (both drugs and biologics)
- 21 CFR 314_NDA (drugs) regulations
- 21 CFR Part 316_Orphan drugs
- 21 CFR 601_Product licensing (biologics)

EMA CMC-Related Guidelines

1. Virus Safety Evaluation of Biotechnological Investigational Medicinal Products (EMEA/CHMP/BWP/398498/05)
2. Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07)
3. Guideline on Plasma-Derived Medicinal Products (CPMP/BWP/269/95)
4. Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004)
5. Annex II to Note for Guidance on Process Validation: Non-Standard Processes (CPMP/QWP/2054/03)
6. Note for Guidance on Manufacture of the Finished Dosage Form (CPMP/QWP/486/95)
7. Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01)
8. CPMP/ICH Guideline Q1A: Stability Testing of New Drug Substances and Products
9. CPMP/ICH Guideline Q5B: Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
10. CPMP/ICH Guideline Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
11. CPMP/ICH Guideline Q5D: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
12. CPMP/ICH Guideline Q6B: Specifications : Test Procedures and Acceptance Criteria for Biotechnological/Biological Products