Review of Chemistry, Manufacturing, and Controls (CMC) of an Investigational New Drug Application (IND)

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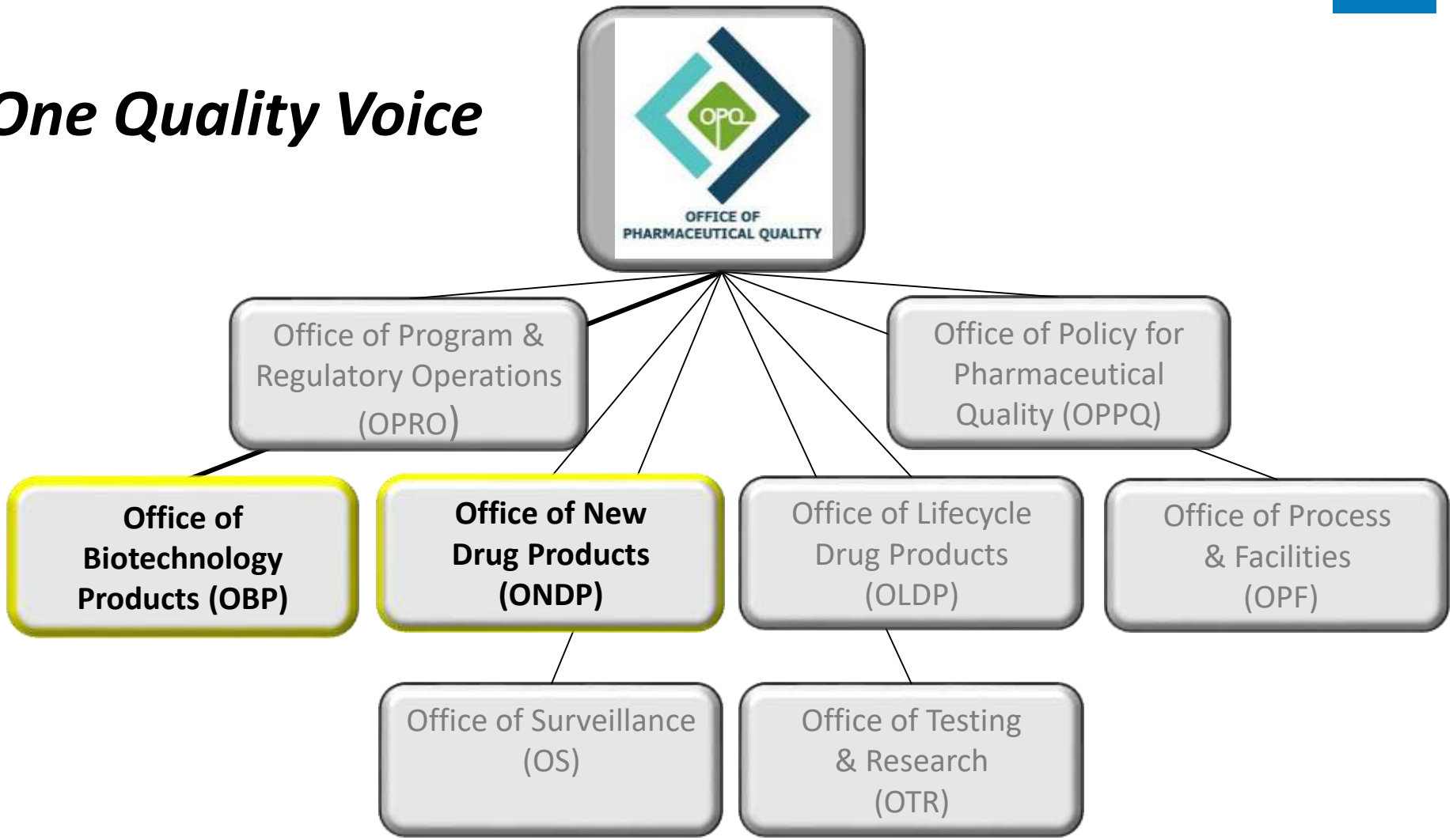
Presentation outline

- Structure of the Office of Pharmaceutical Quality
- Relevance of the CMC information
- Differences between small molecules and biologics
- CMC information, 21 CFR 312.23(a)(7)
- CMC Package
  - Drug substance
  - Drug product
- Case Studies
- Path from IND to a NDA/BLA submission

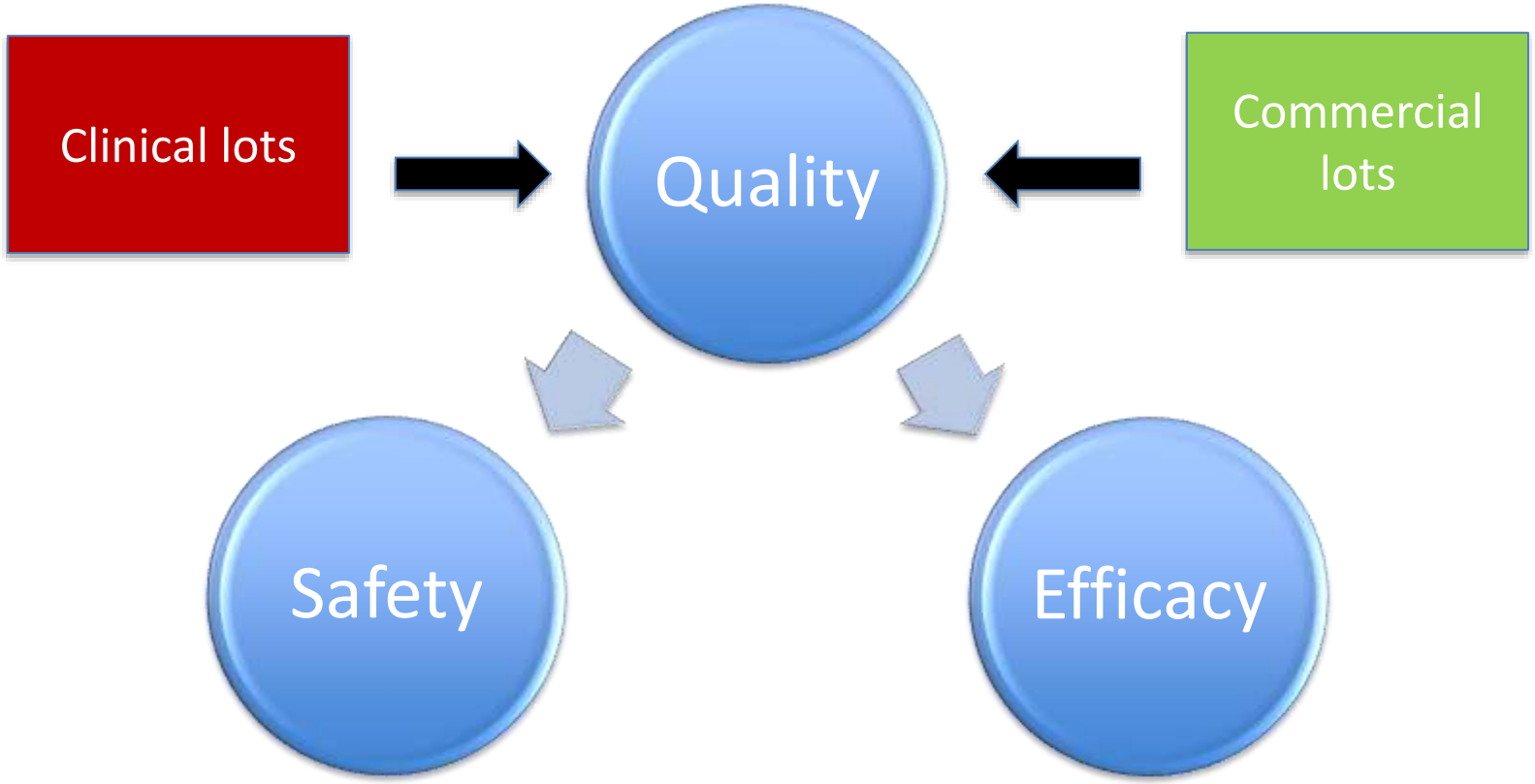
Office of Pharmaceutical Quality

One Quality Voice



The Office of Pharmaceutical Quality assures that quality medicines are available for the American public.

Product Quality



Manufacture of a product of consistent quality assures the clinical performance of commercial lots with regards to safety and efficacy to be the same than the clinical lots

Small molecules vs Biologics

Small molecules

- <900 daltons
- Chemical synthesis
- Semi-synthetics
- Well defined structures
- Regulated under the FD&C

- Purity, safety and strength
- New Drug Application (NDA)
- Reviewed in ONDP

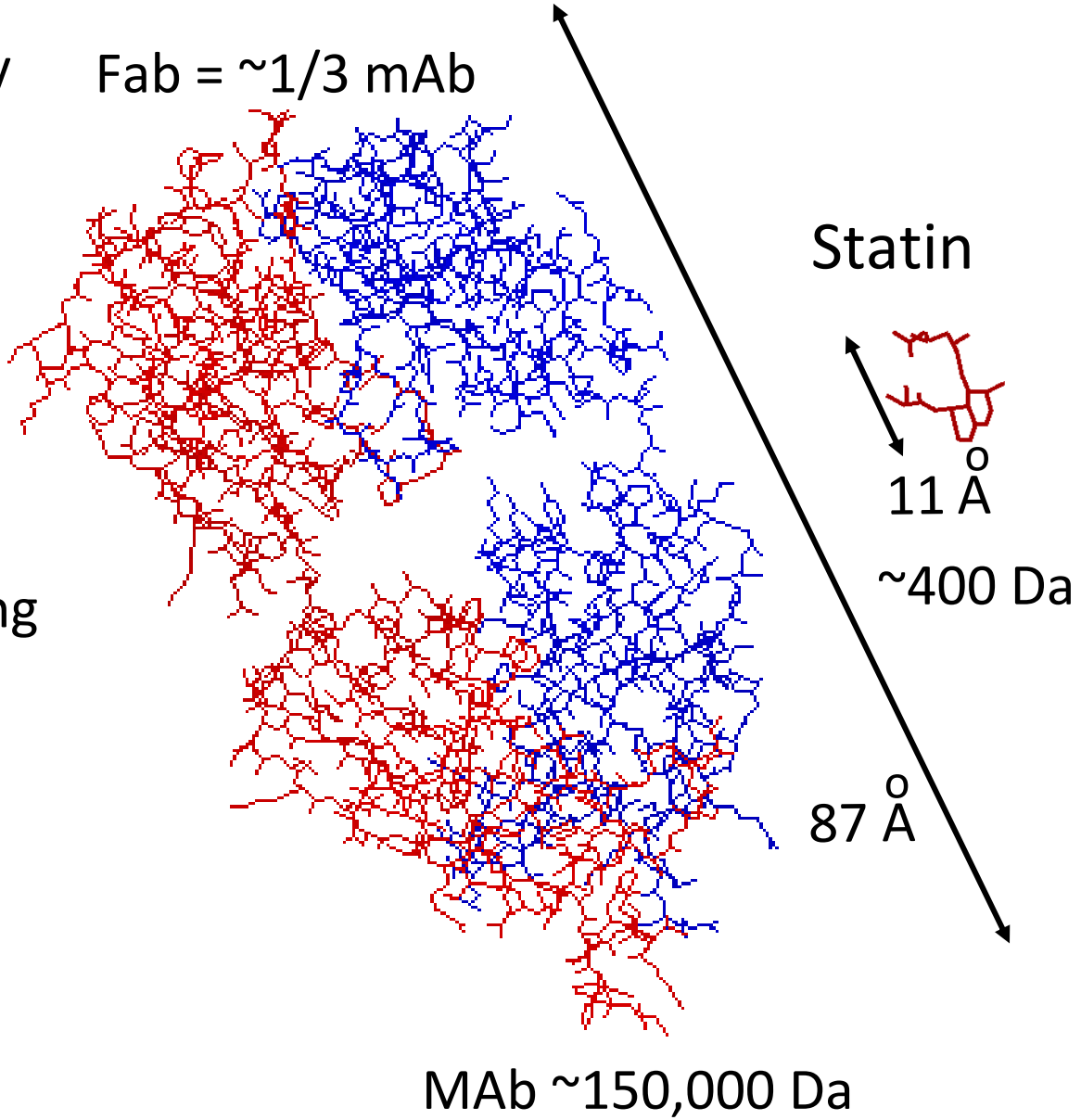
Biologics regulated in CDER*

- Protein > 40 amino acids
- Derived from living material
- Complex structures
- Regulated under FD&C and PHS Act
- Purity, safety and potency
- Biologics License Application (BLA)
- Reviewed in OBP

*For a complete definition of biologics see 21 CFR 600.3

Small molecules vs Biologics

- Size and heterogeneity
- Tertiary structure critical for biological activity
- Sensitive to small changes in manufacturing
- Complex manufacturing processes
- Ability to transmit infectious agents
- Potency
- Immunogenicity



Drugs and Biologics

ONDP Products

- Fermentation products
- Small molecules
- Peptides
- Complex mixtures (heparins)
- Oligonucleotides
- Hormones
- Antibody Drug Conjugates

OBP Products

- Monoclonal Antibodies
- Enzymes
- Growth Factors
- Cytokines
- Toxins
- Fc and Fab Fusion Proteins
- Antibody Drug Conjugates

How the FDA Reviews an IND Application

CFR 312.22: "FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety".

FDA Guidance to Industry: Contents and Format for IND - "… 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 … . The identification of a safety concern or insufficient data to make an evaluation of safety is the only basis for a clinical hold based on the CMC section …".

Pre-submission activities*

Prior to submitting an IND a sponsor can request a Pre-IND meeting to discuss the readiness of their application

- Meeting package with background information
- Focus on specific questions for the review disciplines
- One pre-IND meeting
- CMC
  - Discuss product quality safety issues related to identity, strength, quality, purity, or potency
  - Identify potential hold issues

* Guidance for Industry IND Meetings for Human Drugs and Biologics. Chemistry, Manufacturing, and Controls Information. 2001

CMC Information for INDs

IND content and format: CMC

- Outlined in 21 CFR 312.23(a)(7)
- Description of “composition, manufacture, and control of the drug substance and the drug product”
- Sufficient information to assure “proper identification, quality, purity, and strength”
- The amount of information needed varies “with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available”

CMC requirements for IND

- Drug substance 312.23(a)(7)(iv)(a)
- Drug Product 312.23(a)(7)(iv)(b)
- Placebo 312.23(a)(7)(iv)(c)
- Labels and labeling 312.23(a)(7)(iv)(d)
- Environmental Assessment 25.40, 25.31(e)
- “A brief description of the drug substance and the formulation, including the structural formula, if known” included in the investigator’s brochure 312.23(a)(5)

CMC Package: Drug Substance

Definition

- 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)
  - Not to be used in human subjects

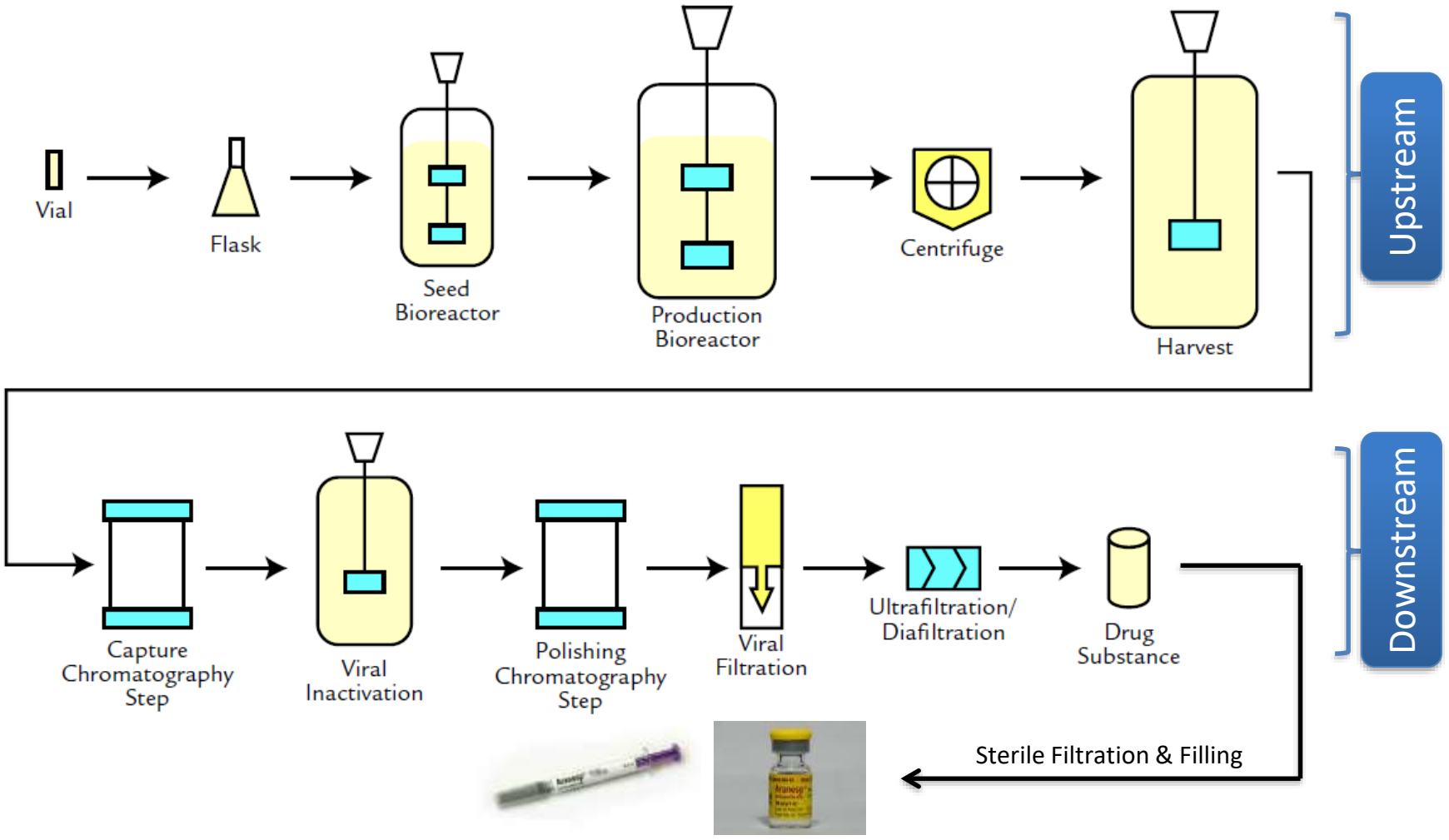
21 CFR 314.3 (b)

Information required

- Description of physical, chemical, or biological characteristics
- Name and address of manufacturer
- Description of the method of preparation/synthesis
- Acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity
- Description of the test methods used
- Information to support stability during toxicology and clinical studies
- Batch analysis data or CoA for clinical and toxicology material

21 CFR 312.23(a)(7)(iv)(a)

Manufacturing process

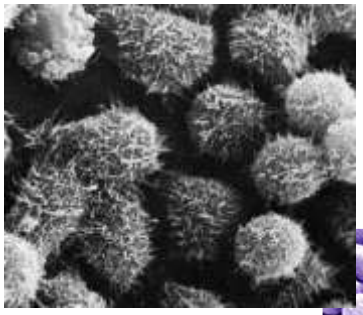


Drug Product

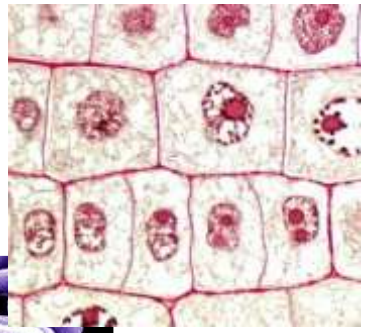
Cell line development

- MCB already developed at time of IND submission
  - Expression vector (DNA plasmid)
  - Information on the parental cell line history
  - Description of the cloning process (Limiting Dilution Cloning, FACS, ClonePix, Clone Select, etc.)
  - Description of assessment, selection and expansion of the final clone

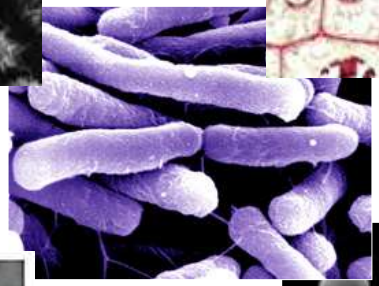
Source Material



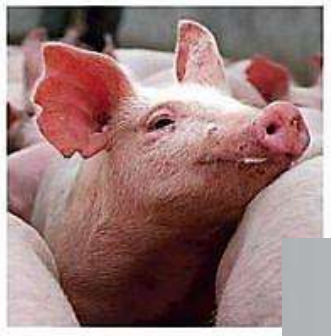
Mammalian



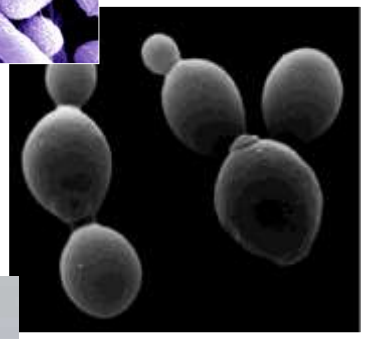
Plant



Bacteria



Pigs



Yeast

Eggs

1. Potential source of adventitious agents contaminants

Bacteria
Mycoplasma
Fungi

Viruses
TSE agents

2. Optimal environment for growth of adventitious agents from raw materials or environment

Testing of the cell bank

- Identity (expected specie, genotypic, phenotypic)
- Purity (bacteria, fungi & mycoplasma contamination)
- Adventitious viruses
  - Test for non endogenous viruses
    - in vitro (cell lines)
    - in vivo (in animals)
    - Antibody production tests (MAP, RAP, HAP)
    - Species-specific tests (based on source material)
  - Test for endogenous viruses (CHO, NS0)
    - Transmission electron microscopy (TEM)
    - Infectivity (Mus dunni, XC & S+L)
    - Reverse transcriptase
    - Other virus specific tests (e.g. PCR)

Sources of Adventitious Agents

- Cell Substrate
  - Endogenous retroviruses
  - Latent or persistent infections
  - May derive from infected animals
  - Established using a viral vector
- Raw material
  - Cell culture reagents (e.g. serum, Trypsin)
- During product manufacturing
  - Handling or equipment
  - Environmental contaminants (water, air)
  - Use of contaminated excipients (e.g. albumin)

Viral safety for Phase 1 IND

- Adequate characterization of cell bank
- Control of raw materials (CoA for RM of biological origin)
  - Documentation that animal derived materials are from Transmissible Spongiform Encephalopathies (TSE) free areas
- Testing of unprocessed bulk
- Screening of cell culture harvest for RVLP from at least 1 lot (CHO, NS0)
- Demonstration of viral clearance by at least 2 orthogonal, robust purification steps in the downstream process
- Safety factor calculation

Viral clearance studies for Phase 1

Demonstrate the capacity of the manufacturing process to clear/inactivate viruses

- Small scale clearance studies
  - Mimic individual purification steps
  - At least two orthogonal, robust purification steps
  - Summary information justifying the appropriateness of the scale down model
  - Calculate log reduction factor

    Spike intermediate material with a model virus

    CHO cell substrate – demonstrate retroviral clearance
  - Calculate safety factor (Estimated Particles/Dose)

Case study 1 – Biologics

Original IND for a recombinant protein produced in CHO

- Two steps evaluated for viral clearance
- Cumulative LRF did not ensure adequate safety margin for potential patient exposure to viral particles
- Insufficient information to demonstrate that the appropriateness of the scale down model

Clinical hold

- Insufficient information to demonstrate:
  - Robust viral clearance capability of the downstream process
  - Acceptable safety margin

Case study 1– Biologics (contd.)

Remove from hold

- Repeat viral clearance studies and evaluated an additional viral clearance step
- Higher cumulative LRV demonstrated
- Acceptable viral safety margin
- Process parameters in scale-down model representative or at worst case compared to the at-scale process

Drug substance characterization

- Physicochemical properties
  - Identity
  - Primary structure
  - High order structure
  - Post translational modifications
  - biological activity
- Immunochemical properties (for antibody Tx)
- Quantity
- Purity, impurities, contaminants

Tabular **and primary data** should be provided

Release/characterization tests

- **Safety**
  - Endotoxin test, bioburden
- **Purity, impurities & Characterization**
  - Reversed-phase HPLC (RP-HPLC), Peptide mapping
  - Mass Spectrometry (MS), Infrared absorption (IR), Nuclear magnetic resonance spectroscopy (NMR), X-Ray diffraction (XRD)
  - SDS-PAGE, Western analysis, capillary electrophoresis
  - Size Exclusion HPLC (SE-HPLC), analytical ultracentrifugation (AUC), field flow fractionation (FFF), light scattering, Capillary isoelectric focusing (cIEF), cation/anion exchange chromatography
  - Hydrophilic interaction chromatography (HILIC)
  - far/near UV circular dichroism, NMR
- **Identity**
  - N-terminal sequencing, peptide mapping, immunoassays (ELISA, Western blotting)
- **Potency**
  - Animal and cell based assays, reporter gene assays, ligand binding (SPR, ELISA) biochemical (enzyme activity)
- **Protein content**
  - Radio immuno assays, ELISA, UV absorbance, Bradford, RP-HPLC

Release specifications

- Subset of characterization testing
- Chosen to *confirm* the quality
- Assure quality, safety, and dosing of future lots (lot-to-lot consistency)
- Specifications include:
  - List of test
  - Analytical procedure
  - Acceptance criteria (numerical limits, ranges, or other criteria)
- Broader early in the development

Release Testing

- Identity
  - Unique/specific for protein/small molecule of interest
- Purity/impurities
  - Sufficient tests to cover major process and product-related impurities
  - Qualified analytical methods
- Potency
  - To assess biological activity of the product (biologics)
  - Assay relevant to protein mechanism of action (biologics)
  - Determine content – Reverse-phase HPLC (small molecules)
- Quantity
  - Protein content
- Microbial safety
  - Bioburden, endotoxin

In- process testing

- Testing of in process material
- Control the manufacturing process
- Monitor the performance of each unit operation
- Action limits
- Assure manufacture of product of the expected quality

Stability testing

- 21 CFR 312.23 (7)(ii) …"stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation…".

- 21 CFR 312.23(7)(iv)(a) "…information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies"

Stability testing

- Stability under recommended storage conditions
  - Stability protocol (test, acceptance criteria and testing schedule)
  - Subset of release assays: stability-indicating assays, including potency assays
- Stability under accelerated (elevated temperature) conditions
- Stability under stress conditions (degradation pathways)
- Amount of stability data is phase-dependent
- Place the toxicology and the first GMP lot on stability
- Collect stability data throughout clinical development

Case study 2 – Biologics

Original IND submission for a recombinant protein

- Stability data provided only for the toxicology lot
- No stability data for the proposed clinical lot

Issue

- The toxicology lots showed a time-dependent increase in impurities by Reversed-Phase HPLC through 6-months of storage under recommended storage conditions of -70°C

Case study 2– Biologics (contd.)

Clinical Hold

- No assurance that the proposed clinical lot would remain stable throughout the planned duration of clinical study

Remove from hold

- Provide sufficient real-time stability data, including primary data (chromatograms, gels images) for the clinical lot to ensure stability during the clinical study

CMC information for phase 1 Safety, Safety, Safety

- Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury [312.42(b)(1)(i)]

- The IND does not contain sufficient information required under 312.23 to assess the risks to subjects of the proposed studies [312.42(b)(1)(iv)]

CMC Safety Concerns

Nature of the molecule (API):

- Elicits adverse effects: toxin
- Blocks signaling pathways: immunomodulator
- Ab-Toxin fusion/conjugates: mis-targeting
- Mutagenic with potential for carcinogenic risk

Presence of Impurities:

- Process related impurities (Host cell proteins/DNA)
- Product related impurities (aggregates, product variants)

General Safety Concerns:

- Bioburden
- Endotoxin
- Viruses
- Sterility (DP)
- Elemental impurities
- Residual solvents

CMC Safety Assessment

- Safety evaluation of the clinical material is based on nonclinical study results
  - Pharmacological effects
  - Toxicology effects
  - Proof of concept
  - Initial safe dose

  Nonclinical safety data is leveraged to support the safety of the propose clinical lot

- Is the nonclinical material representative of the clinical material?

Comparability of Toxicology and Clinical Lot

- Comparison of the manufacturing process between the toxicology and the proposed clinical lot
- Analytical comparison between the toxicology and phase I clinical material
  - Risk based
  - Tabular and primary comparability data (reproductions of gels, chromatograms)
  - Side by side analysis preferred
  - Focus on quality attributes related to safety
    - Process and product related impurities
    - Potency

Case study 3– Biologics

Original IND submission for a recombinant protein

- Release results for the toxicology and clinical material met the release acceptance criteria
- Only tabular data provided in the IND
- Request for high quality primary data (gels, chromatograms, etc.) for the toxicology and clinical material

Issue

- Differences in purity profile by SDS-PAGE (gel images)
  - High and low molecular weight bands not observed in tox lot
  - Not detected by western blot (not product related)

Case study 3– Biologics (contd.)

Clinical Hold

- Insufficient data to support comparability between the toxicology and clinical material

Remove from hold

- Explain the nature of the high and low molecular weight bands observed in the clinical material and their potential impact on patient safety

Immunogenicity – Anti-drug antibodies (ADA)

- ADA are a safety concern
- Need to be assessed/measured
- Develop/validate immunogenicity assays
  - Binding antibody assay
  - Neutralizing antibody assay

Hold Issues – Biologics

- Proposed clinical lot has not been manufactured
- Insufficient characterization of cell banks
- Insufficient data to support viral clearance
- Insufficient data to support comparability between toxicology and proposed clinical lots
- Inadequate specifications for release and stability testing
- Lack of information for raw materials of animal origin
- Insufficient data to support product stability for the duration of the clinical studies
- Lack of evidence for final drug product sterility

Hold Issues – Biologics (contd.)

- High levels of process-related impurities
- Endotoxin at higher doses > 5 EU per kg per hour
- Product lacks potency assay
- Product lacks adequate characterization

U.S. FOOD & DRUG ADMINISTRATION

Review of CMC of an IND

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Office of New Drug Products, OPQ

Poll: Proper Term

What is your preferred term for the molecule investigated in an IND?

- Investigational Product
- Investigational Drug
- Study Drug
- Clinical Trial Material
- Drug Product

Presentation Outline

- Structure of the Office of Pharmaceutical Quality
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- Differences between small molecules and biologics
- CMC information, 21 CFR 312.23(a)(7)
- CMC Package
  - Drug substance
  - Drug product
- Case Studies
- Path from IND to a NDA/BLA submission

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

Dosage Forms

Drug Product Section

- Components: Actives and inactive(s)/excipients
- Quantitative composition
- Manufacturer (name and address)
- Description of manufacturing and packaging process
- Batch analysis
- Analytical methods

Drug Product Section (Contd.)

- Container/closure system
- Specification (tests, analytical procedures and acceptance criteria)
- Stability data
- Label and Environmental Assessment
- Placebo

Excipients

- Pharmacologically inactive
- Binders, fillers, disintegrants, lubricants, solubilizers, flavoring agents, bulking agents, preservatives, stabilizers, salts, etc.
- - binders achieve the “hardness” of the tablet
- - taste masking (Pediatric formulations)
- - preservative (multi-dose products)
- - bulking agents (lyophilization)

Excipients (contd.)

- surfactants (surface adsorption, aggregation)

- sugars, salts (osmotic potential/tonicity, cryoprotectants)

- Excipients may serve many functions
- Two or more excipients may be necessary to obtain the desired property
- Quality: Compendial vs non-compendial

Excipients (contd.)

- Suitability for intended use
- Functionality
- Compatibility with drug substance and other components
- Safety/performance issues
- Source (USP/NF; FDA Inactive Ingredients Database)

Excipients (contd.)

- 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>

Manufacturing

Small Molecule

Weigh Active & Inactive(s)

↓

Sieve/Blend

↓

Capsule fill

Biologics

Thaw and/or pool bulk drug substance (if needed)

↓

Formulation (if needed)

↓

Sterile filtration (0.2μ)

↓

Aseptic fill/finish

↓

Lyophilization as needed

Case Study

- Dosage Form: Capsule
- Formulation presented in CMC Section: API + Filler A (excipient)
- Formulation presented in Investigator's Brochure: API + Filler B (excipient)

Check CMC section and IB to ensure consistency (formulation & storage conditions)

Drug Product Specification

- Defined in ICH Q6A as:
  - "…a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use

- Includes attributes that serve as surrogates for performance

Critical Quality Attributes

By a show of hands:

How familiar are you with Critical Quality Attributes?

a) Very familiar

b) Somewhat familiar

c) Not familiar

Critical Quality Attributes

- "A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality"
  - ICH Q8 (R2)

Critical Quality Attributes

- Safety perspective
  - Impurities
  - Sterility
  - Endotoxin limits
  - Immunogenicity
  - Particulate matter

Drug Product Specification

Attribute	Acceptance Criteria (typical values)	Analytical Procedure (for example)
Identity	Matches Standard	IR or HPLC/UV
Appearance	Color, Imprint	Visual
Assay	90-110%	HPLC
Dose Uniformity	Statistical Criterion (USP)	HPLC or Weight
Release from Dosage Form	80% in 15 or 30 minutes	Stirred Aqueous Vessel
Impurities (Related Substances)	<1% to few %	HPLC
Microbial Limits Or Sterility	# of total aerobes and fungi per gram Pathogen (-)	Growth in special media
Water Content	Few %	Chemical or wgt. loss
Preservative Content	NLT 75% of Initial	HPLC

Drug Product Specification Biologic

Attributes	Analytical Procedure	Acceptance Criteria
Peptide profile (Identity)	Peptide Mapping	Comparable to reference
Monomer (Purity)	Size exclusion HPLC	≥ 90.0% monomer
Heavy chain + Light Chain (Purity)	CGE (reducing)	≥ 90.0% IgG as heavy + light chain
Relative Potency (Biological activity)	Binding ELISA	50% - 150% potency relative to reference
Specific activity	Binding ELISA	500 – 1500 U/mg
High molecular mass species (HMMS) -Impurities	Size exclusion HPLC	≤ 5.0% HMMS
Fragments (impurities)	CGE Reducing	Comparable to reference standard with no new peaks
Endotoxin	USP <85>	≤ 0.25 EU/mg
Sterility	USP <71>	No growth detected

Case Study

- Study Drugs: 3 IV products (all US Approved)
- Preparation: Mix the 3 products
- Issues:
  - No testing of the final solution
  - Compatibility not demonstrated

Recommended Quality tests: Assay for individual drug, impurities (no change in profile and levels), particulate matter, and sterility.

Container Closure System

- The sum of packaging components that together contain, protect, and deliver the dosage form (primary and secondary packaging components)
- 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

By a show of hands:

How much stability data is required to support an IND?

a) Per ICH recommendations

b) None

c) Not sure

Stability

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

Stability Data (contd.)

- The amount of data will depend upon the duration of the proposed clinical study
- To support investigational studies
- To ensure that the quality and safety of the investigational drug is maintained throughout the clinical trial period
- To obtain impurity profile of the batches used during non-clinical toxicological studies
- Understand degradation pathways of product
- Identify stability indicating assays

Expiration Dating Period

By a show of hands:

Do clinical trial materials have an expiration date?

a) Yes

b) No

c) Maybe

Expiration Date

- Expiration dating period is not required for the clinical trial materials
- Reconstituted drug 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"

Case Study

- Study Drug: Lyophilized powder for injection
- Preparation:

  - reconstitute lyophilized powder with a diluent

  - Diluted further with the recommended diluent

Issues:

- No in-use testing for quality (assay, impurities, particulate matter etc.) of the diluted solution to support the recommended storage condition.

Placebo

- Formulation identical to the study drug but without the active
- Shape, size, color to mimic the study drug
- Complete CMC information – composition, manufacture, specification (include a test to show absence of active) and stability testing.

  - 21 CFR 312.23 (a) (7) (iv) (c):

Label

The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use”

- 21 CFR 312.6 (a)

Environmental Analysis

Claim for categorical exclusion from Environmental Assessment

- 21 CFR 25.31(e)

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 Harmonization of Technical Requirements for Registration Of Pharmaceuticals for Human Use Guidance E6, "Guideline for Good Clinical Practice" http://bit.ly/E6-GCPs and 21 CFR 312.62

IND Review Output

- No Safety concerns: Safe to proceed with proposed trial
    - "non-hold" comments and/or recommendations to consider during drug development
- Safety concern(s) – placed on hold until outstanding issues are satisfactorily resolved

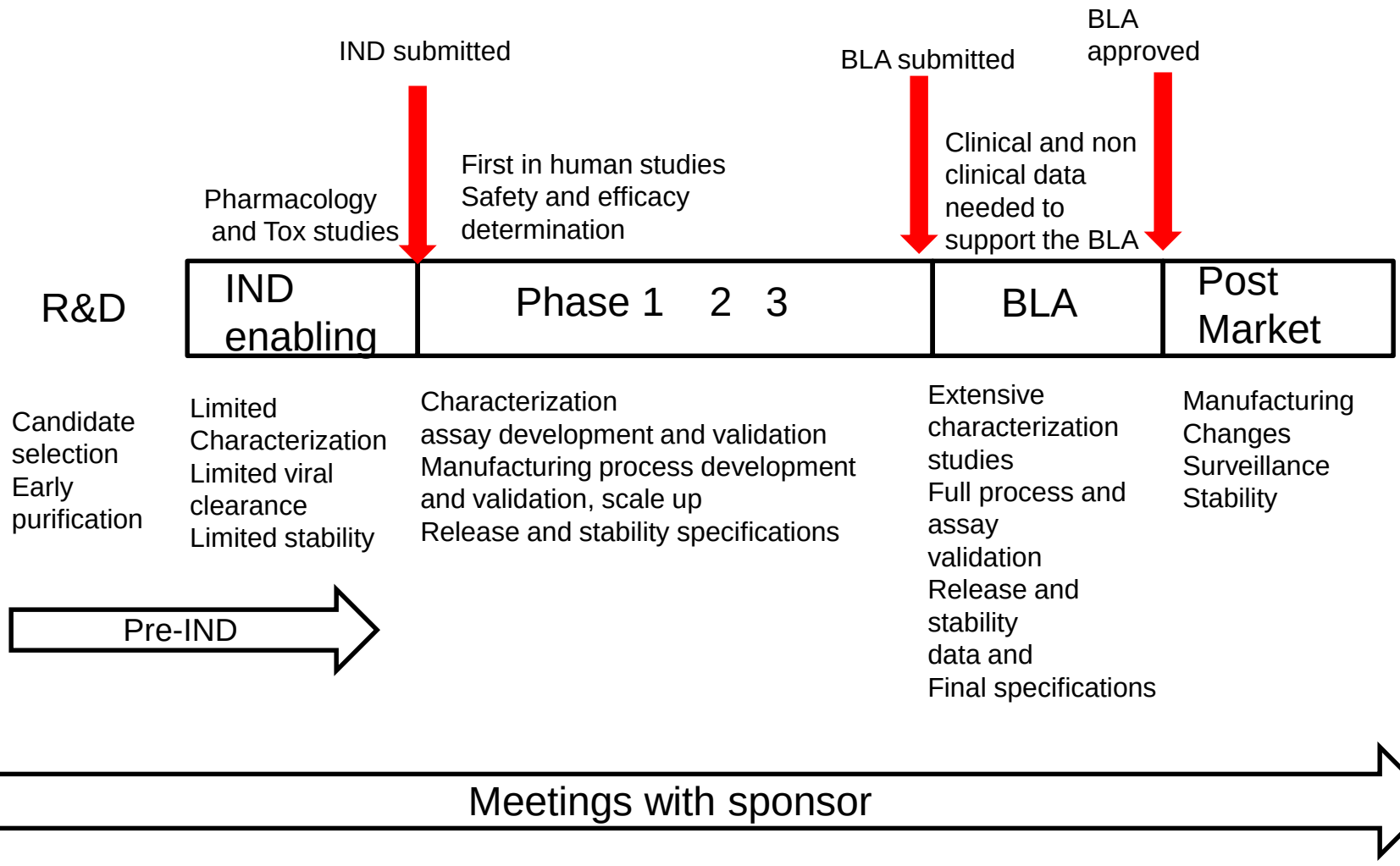
IND maintenance-CMC

- Include information without the scope of a protocol amendment, safety report or annual report, 312.30
- The sponsor can amend the IND at any time
- CMC amendments
  - Changes in manufacturing process or sites
  - Assays (addition or changes)
  - Additional characterization data
  - Additional information is expected as IND moves to Phase 2 and 3

IND Maintenance (contd.)

- IND can go on hold if the information in the amendment is not sufficient to ensure safety
- Annual report, information gathered during a calendar year, not reported in amendments
  - For CMC, often stability data updates

Product Lifecycle



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
- 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
- CGMP should be applied - Phase 1 drugs do not need full CGMP but do need good manufacturing controls
- Recommendations of ICH/FDA guidances and input from FDA are helpful during drug development

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

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

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)

Questions?

Please complete the session survey:
surveymonkey.com/r/DRG-D1S05

Thank you!