Chemistry, Manufacturing, and Controls (CMC) information for an Investigational New Drug Application (IND)

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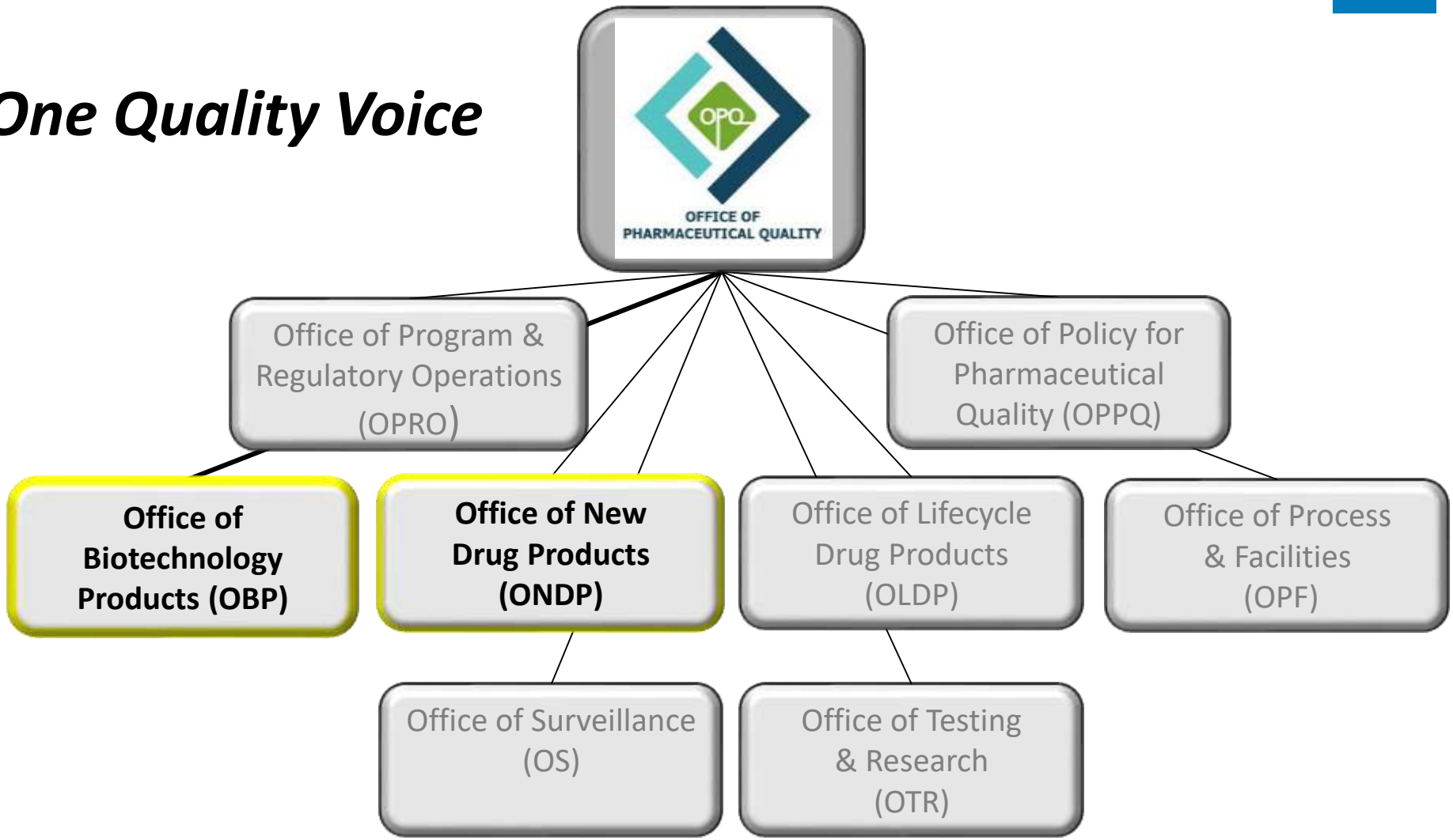
Presentation outline

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

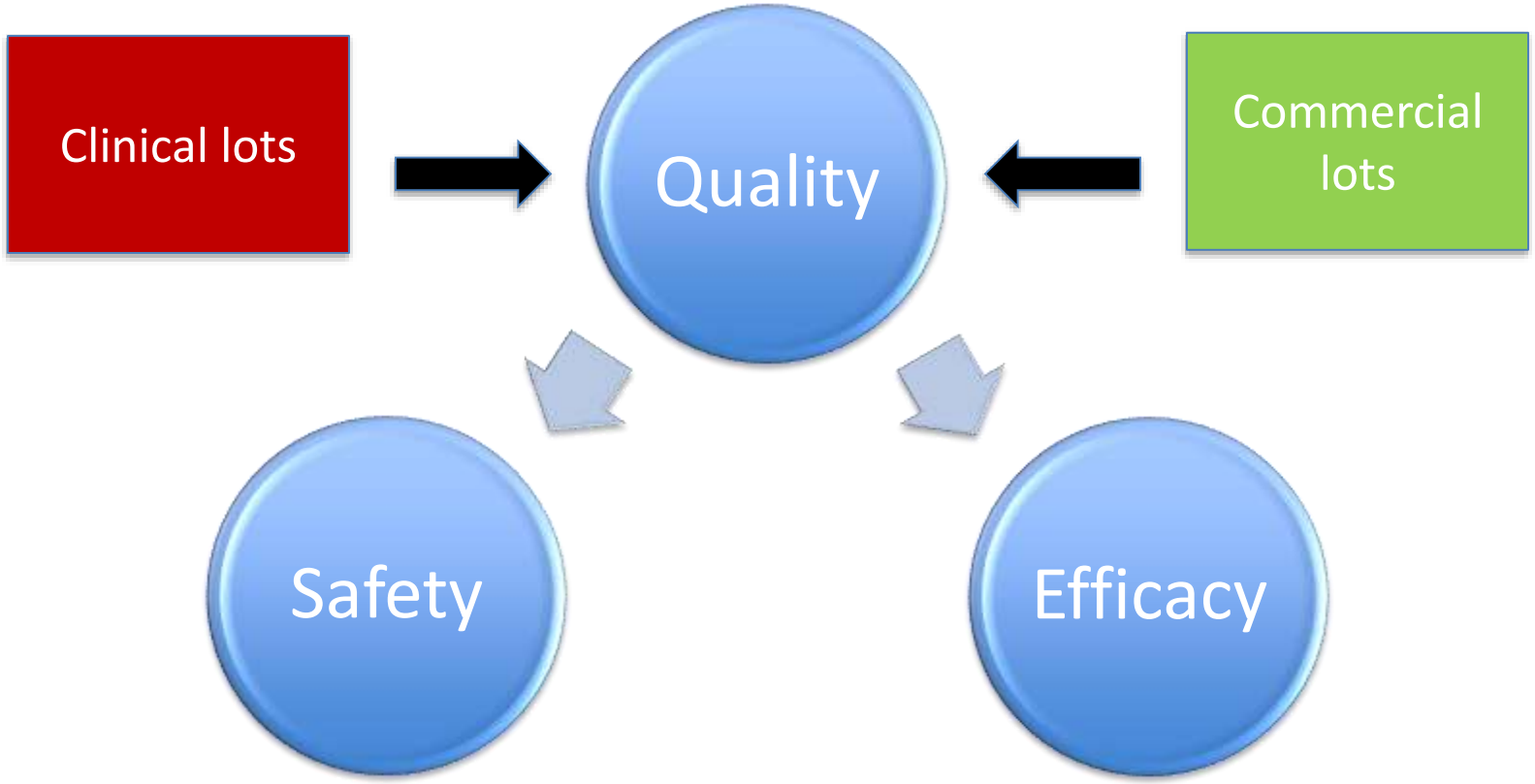
Office of Pharmaceutical Quality

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

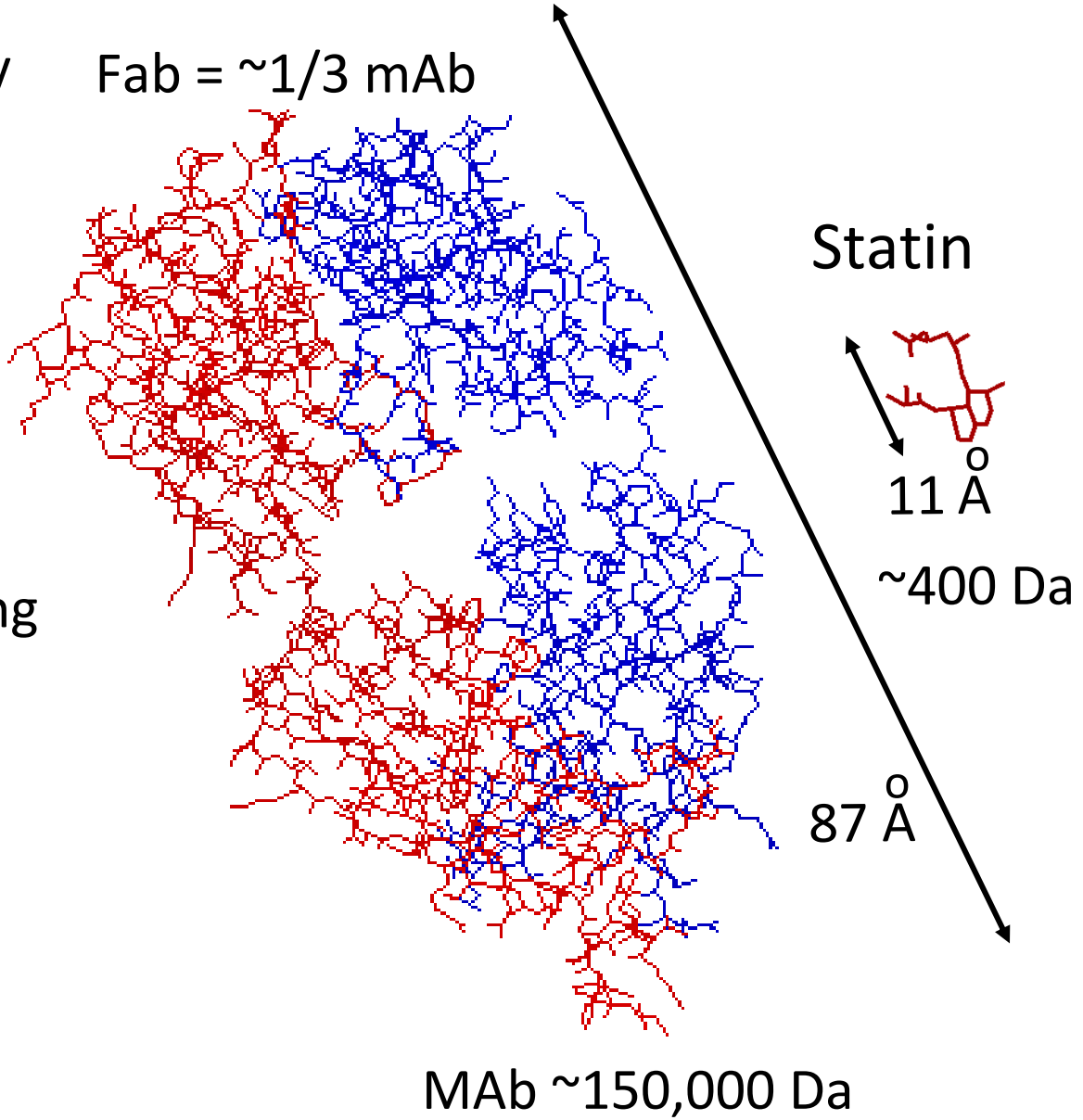
Biologics regulated in CDER*

- 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

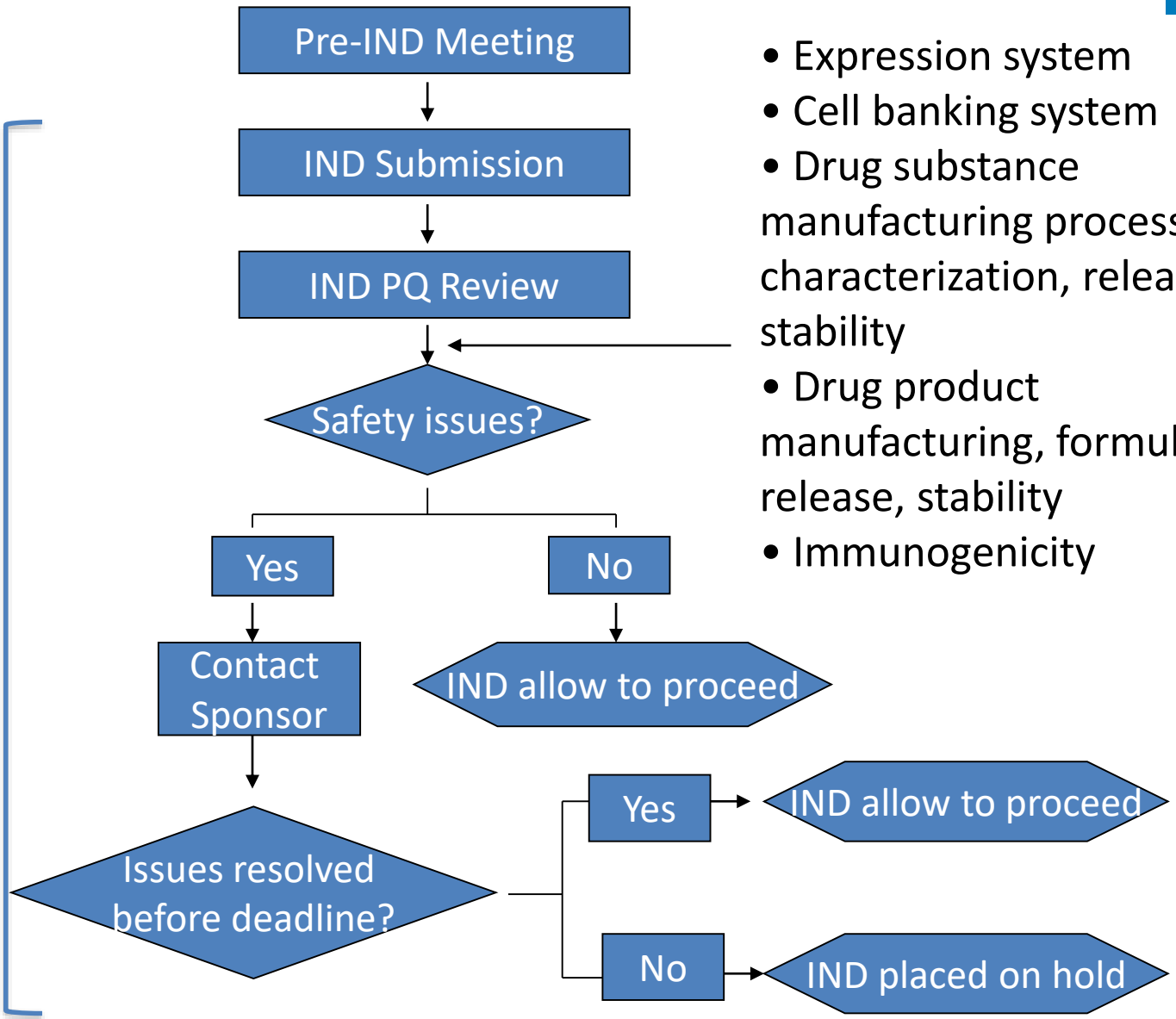
Small molecules vs Biologics

- 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



IND Review Process

30 days timeline
21 CFR 312.40



- Expression system
- Cell banking system
- Drug substance manufacturing process, characterization, release, stability
- Drug product manufacturing, formulation, release, stability
- Immunogenicity

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

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".

CMC bases for Clinical Hold

- 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)]

FDA may place an IND on clinical hold at any time during development

CMC Information for INDs

IND content and format: CMC

- Outlined in 21 CFR 312.23(a)(7)

312.23(a)(7)(i) emphasize the graded nature of manufacturing and controls information:

“ Although in each phase of the investigation sufficient information should be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary 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)

Phase 1

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 …".

Data required to assess the safety of the drug product at each phase of development is product specific.

CMC Safety Assessment

FDA Guidance to Industry: Contents and Format for IND "... for pre-clinical studies to be useful in assuring the safety of human studies, sponsors should be able to *relate* the *drug product* being proposed for use *in a clinical study* to the drug product used in the *animal toxicology studies that support the safety* of the proposed human study".

Is the nonclinical material representative of the clinical material?

Comparability of Toxicology and Clinical Lot

- Manufacturing process
- Analytical comparability
  - Risk based
  - Tabular and primary comparability data (reproductions of gels, chromatograms)
  - Focus on quality attributes related to safety
    - Process and product related impurities
    - Potency

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

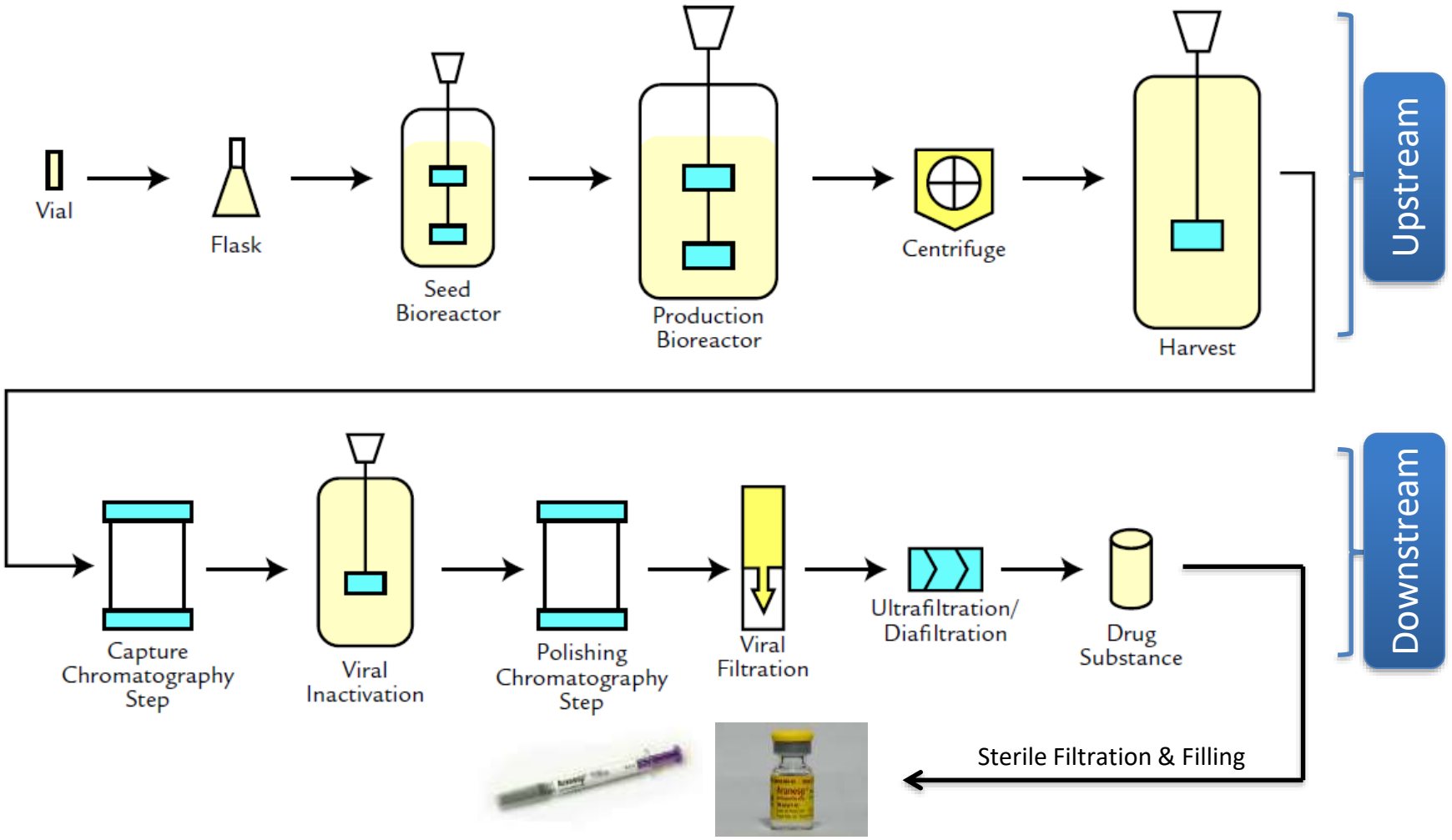
21 CFR 314.3 (b)

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

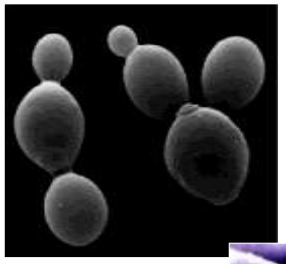
21 CFR 312.23(a)(7)(iv)(a)

Manufacturing process

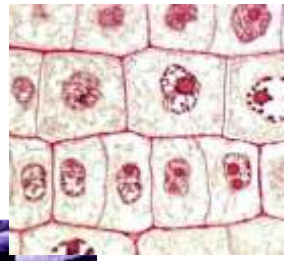


Drug Product

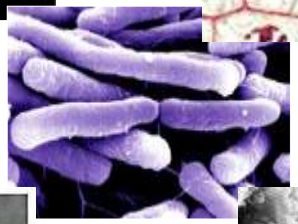
Cell substrate development



Yeast



Plant



Bacteria

Pigs

Mammalian

Eggs

Bacteria
Mycoplasma
Fungi

Viruses
TSE agents

- Cell bank already developed at time of IND submission
- Test for identity
- **Testing for adventitious agents is critical**
  - Potential source of adventitious agents contaminants
  - Optimal environment for growth of adventitious agents from raw materials or environment

Viral safety for Phase 1 IND

- Testing of cell bank for adventitious viruses
  - Endogenous
  - Non- endogenous
- Control of raw materials
  - List of the raw materials and their sources (animal, plant, recombinant).
  - Source country for animal derived materials
  - Letters from suppliers verifying that animal derived materials came from BSE free countries
- Testing of unprocessed bulk for purity
- Screening of cell culture harvest for RVLP from at least 1 lot (CHO, NS0)

Viral safety for Phase 1 IND (contd.)

- Viral clearance studies
  - Demonstrate of the capacity of the manufacturing process to clear/inactivate viruses
  - At least 2 orthogonal, robust purification steps in the downstream process
  - Performed at small scale
  - Summary information justifying the appropriateness of the scale down model
  - 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

Upstream manufacturing process

- Description of the fermentation and harvesting processes
- Description of process controls and limits
- Unprocessed bulk testing results
- Hold times

As development proceeds, establish in-process controls and set alert/action limits

Downstream manufacturing process

- Description of the purification process including process controls and limits
- Removal and/or characterization of process related impurities
  - HCDNA
  - HCP
  - Antibiotics
  - Induction agents
  - Detergents, etc
- Removal and/or characterization of product related species
  - Aggregates, clipped products, charge variants, etc

- Develop methods to test and compare impurities across lots

Process development

- As development proceeds increase degree of control of the manufacturing process
- Identify critical process parameters and establish in-process controls with alert/action limits and critical hold times
- Establish the manufacturing process prior to manufacture of Phase 3 material

Submit Amendments to the IND after significant changes in manufacture in a timely manner

Drug substance characterization

- Physicochemical properties
  - Identity
  - Primary structure
  - High order structure
  - Post translational modifications
  - biological activity
- Quantity
- Purity, impurities, contaminants

Drug substance characterization

The product does not need to be pure or fully characterized to enter clinical trials,

but

We need to be able to compare lots to apply the pre-clinical (animal tox) and early (phase 1/2) safety and dose-finding data to later (phase 2/3) clinical trials

Develop/identify as early as possible, relevant release, characterization and stability indicating assays that are sensitive and precise

Assays should be validated prior to licensure

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 Testing

- Subset of characterization tests that measure key features of the drug substance and can be performed routinely
- 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
- 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

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

- Identify stability indicating tests that confirm the stability of the DS under the recommended storage
- Provide data to support the stability of the DS for the duration of the toxicology and clinical studies
- Develop stability protocols under recommended, accelerated and stress storage conditions
- The container for storage of DS stability samples should be representative of the DS container used to store pre clinical and clinical material
- Place the toxicology and the first GMP lot on stability
- Collect stability data throughout clinical development

In-use Stability (Drug Product)

- The IND should include data to support:
  - Product stability during handling and administration (e.g. aggregation, potency)
  - Compatibility of the product with the delivery system
- Studies should be performed under the conditions

For highly potent products (e.g. bispecific antibodies, ADC, etc.) administered at very low doses, data to support adequate recovery of product from the infusion bag is critical

Case study 2 – Recovery

Original IND submission for an Antibody-Drug conjugate (ADC) administered by IV infusion

- Proposed doses: 0.01, 0.05, 0.25, and 1.00 mg/kg
- Recovery data (simulated) for the low and high dose in saline and 5% dextrose using the administration set

	D5W (inline filter)				Saline (inline filter)			
	% Recovery (ECL)							
Dose (mg/kg)	0.01	0.05	0.25	1.00	0.01	0.05	0.25	1.00
T0 (pre/post filter)	61/86	70/97	91/98	89/92	25/55	71/92	80/87	86/89
T4 (pre/post filter)	70/68	85/96	N/T	N/T	40/44	69/72	N/T	N/T
T24 (pre/post filter)	71/83	70/86	88/93	94/96	33/51	64/77	86/85	92/86

Case study 2 – Recovery (Contd.)

Issue

- No assurance that patients would receive the intended dose, particularly at the lower doses
- Unreliable safety information collected
- Inappropriate dose escalation

To address the deficiency

- Data to support product recovery using the proposed administration material
- Identify the factors contributing to the low protein recovery
- Implement a strategy to ensure consistent protein recovery at doses used in clinical studies

Case study 3 – 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 3– 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

Case study 4– 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

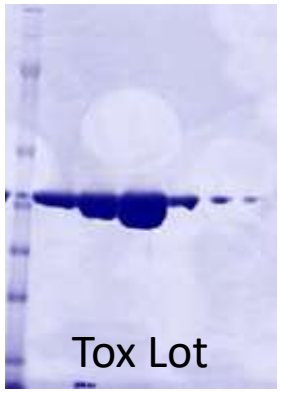
Issue

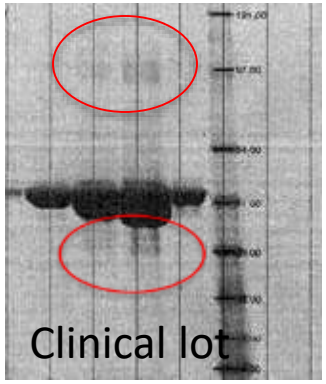
- Differences in purity profile by SDS-PAGE (gel images)
  - High and low molecular weight bands not observed in tox lot
  - Not detected by western blot (not product related)

Case study 4– 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

The biggest immunogenicity concern is potential cross-reactivity of ADA response with non-redundant endogenous protein (deficiency syndrome)

Common CMC Hold Issues

- No clinical product manufactured
- Insufficient characterization of cell banks
- Insufficient data to support viral clearance
- Insufficient data to support comparability of toxicology and proposed clinical lots
- Lack of potency assay
- Inadequate specifications for release and stability testing (report results)
- Lack of information for raw materials of animal origin
- Insufficient stability data
- No endotoxin or sterility testing

Poll: Which is **NOT** a hold issues for a phase 1 IND

A. Lack of primary data to support comparability of toxicology and clinical lot

B. Release and stability assays are not validated

C. No testing of the cell bank

D. Lack of potency assay

Poll: What is a reason to put an IND on hold?

A. Safety

B. Efficacy

C. Insufficient information to assess risk to subjects

CMC Information for an Investigational New Drug (IND) Application

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Office of New Drug Products,
OPQ/CDER/FDA

Presentation Outline

- Structure of the Office of Pharmaceutical Quality
- Relevance of the CMC information
- Small molecules and biologics
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- CMC package
  - Drug substance
  - Drug product
- Case studies
- Path from an 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

Drug Product Section

- Component: actives and inactives/excipients
- Quantitative composition/Quality
- Manufacturer (name and address)
- Description of manufacturing and packaging process

Drug Product Section (Contd.)

- Specification (tests, analytical procedures and proposed acceptance criteria)
  - ✓ CoA of the clinical batch
- Container/closure system
- Stability data

Drug Product Section (Contd.)

- Label
- Environmental assessment
- Placebo

Excipients

- Pharmacologically inactive
- Suitability for intended use
- Functionality
- Two or more excipients may be necessary to obtain the desired property
- Quality: compendial *vs* non-compendial

Excipients (contd.)

- Compatibility with drug substance and other components
- Safety/performance issues
- Source (USP/NF; FDA Inactive Ingredients Database)
- Excipients of human or animal origins
- Novel excipients*

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

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)

Manufacturing Process Examples

Small Molecule

Weigh active & inactive(s)

↓

Sieve/blend

↓

Granulation and milling

↓

Drying and compression

↓

Tablet film coating

Biologics

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

↓

Formulation (if needed)

↓

Sterile filtration (0.2μm)

↓

Aseptic fill/finish

↓

Lyophilization as needed

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

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)

Drug Product Specification Example

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 Example

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

Container Closure System - Quality Considerations

- Water / Moisture / Humidity
- Light
- Oxygen
- Temperature
- Contaminants in primary packaging component
- Leachables (primary or secondary component)
- Microbial contamination
- Sterility assurance

Question: Stability

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

The Use of Stability Data

- 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

Expiration Dating Period

- 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)

IND Review Output

- No Safety concern: safe to proceed with the 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

CMC Safety Concerns

(potential “hold” issues)

- Product made with unknown or impure components
- Chemical structures of known or likely toxicity
- Impurity profile is insufficiently defined or indicates a risk or exceeds levels qualified through toxicology studies.
- Lack of sterility assurance or endotoxin control (e.g., injectable drug products)
- Product not stable through clinical study duration

IND Maintenance-CMC

- Include information without the scope of a protocol amendment, safety report or annual report, 21 CFR 312.30
- The sponsor can amend the IND at any time
- IND can go on hold if the information in the amendment is not sufficient to ensure safety

IND Maintenance (contd.)

CMC amendments

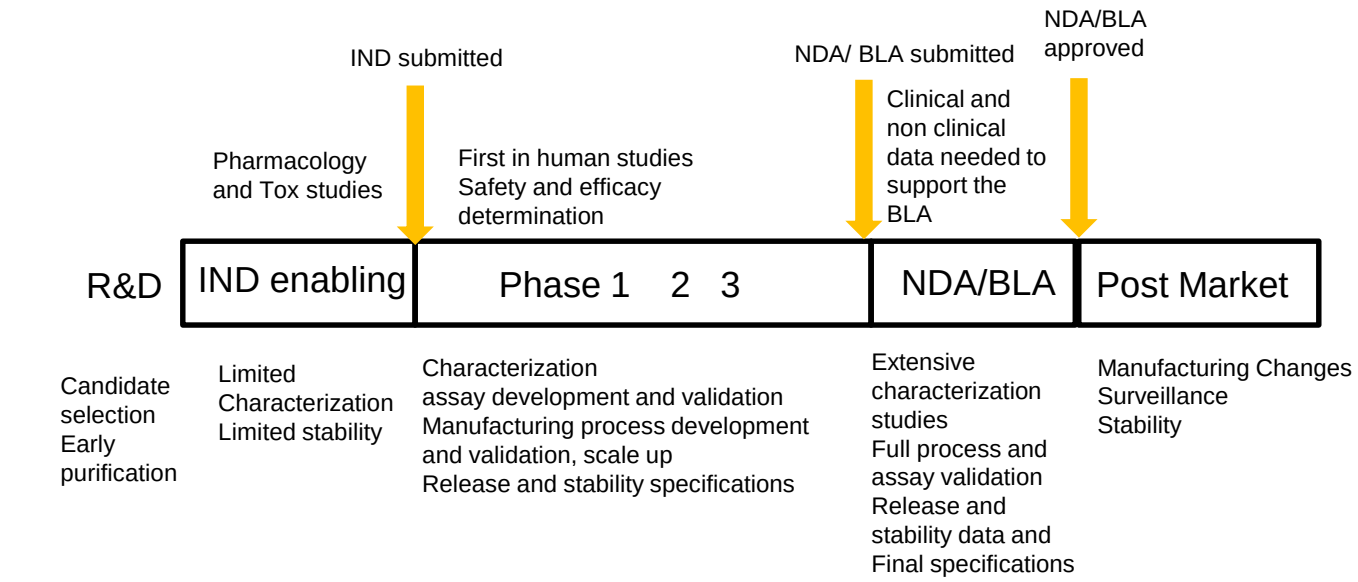
- Changes in manufacturing process or sites
- Change in the container closure system affecting product quality
- Change in the method of sterilization
- Additional information is expected as IND moves to Phase 2 and 3

IND Maintenance (contd.)

Annual report (AR), information gathered during a calendar year, not reported in amendments, CFR 312.33(b)(7)

- "A summary of any significant manufacturing or microbiological changes made during the past year"
  - For CMC, often stability data updates

Product Lifecycle



FDA IND Guidance

- "Content and Format of INDs for Phase 1 Studies of Drugs, Including well—characterized, therapeutic Biotechnology-derived products" (1995)
- INDs for Phase 2 and 3 Studies-Chemistry, Manufacturing, and Controls Information" (2003)
- "Formal Meetings Between the FDA and Sponsor or Applicants of PDUFA products" (2017)
- "IND meetings for human Drugs and Biologics-Chemistry, Manufacturing, and Controls information" (2001)
- "CGMP for Phase 1 Investigational Drug" (2008)

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

Questions?

Please evaluate this session:

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