Regulatory perspectives on the manufacture and characterization of biotechnology products during pharmaceutical development

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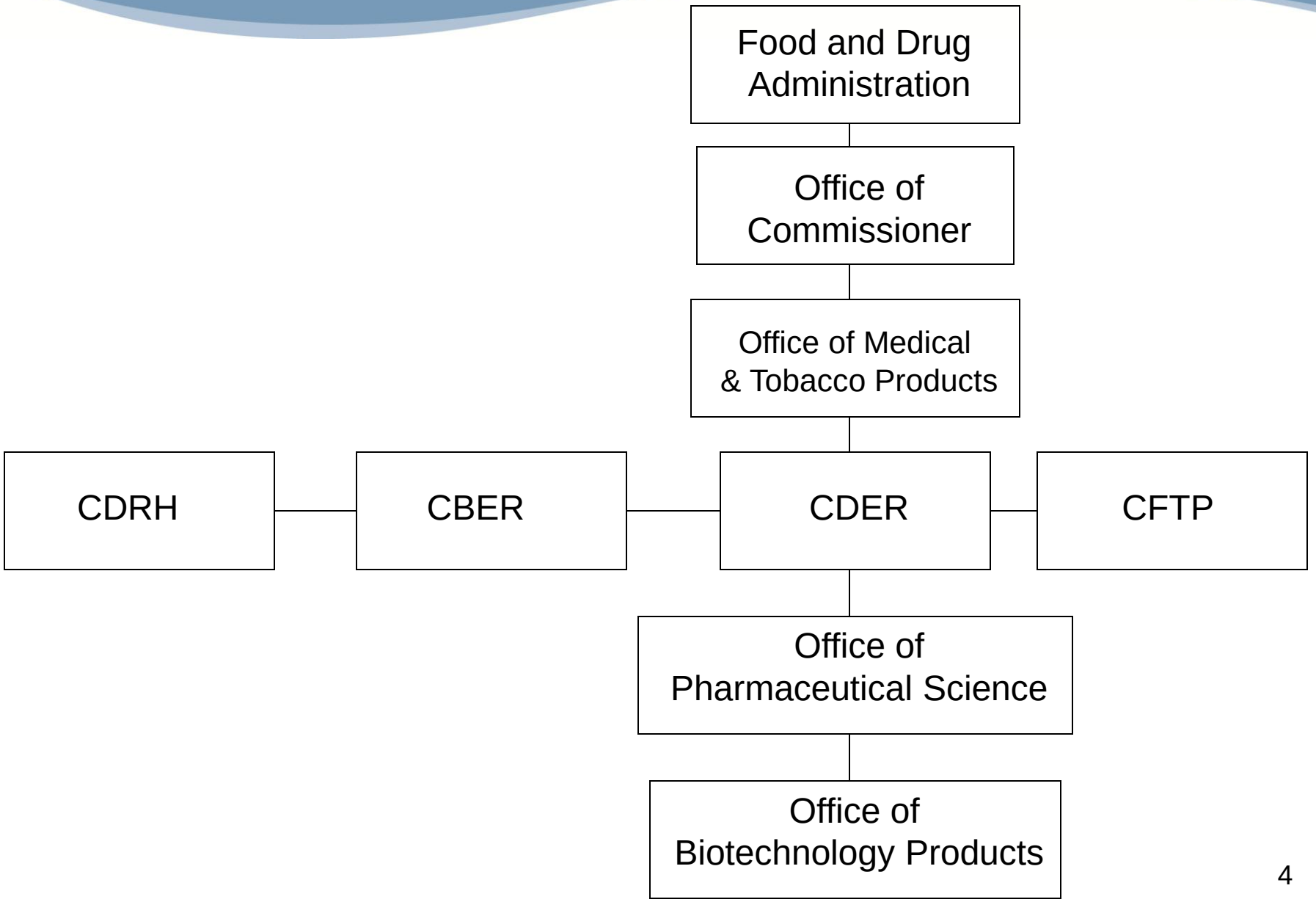
The views and opinions expressed here are my own and should not be used in place of regulations, published FDA guidance's or discussions with the Agency.

Outline

- Therapeutic proteins and their unique attributes
  - Product complexity
  - Complex manufacturing
- Things to consider when developing a biotech product
  - Product characterization
  - Product manufacturing
  - Immunogenicity
  - Communication with the FDA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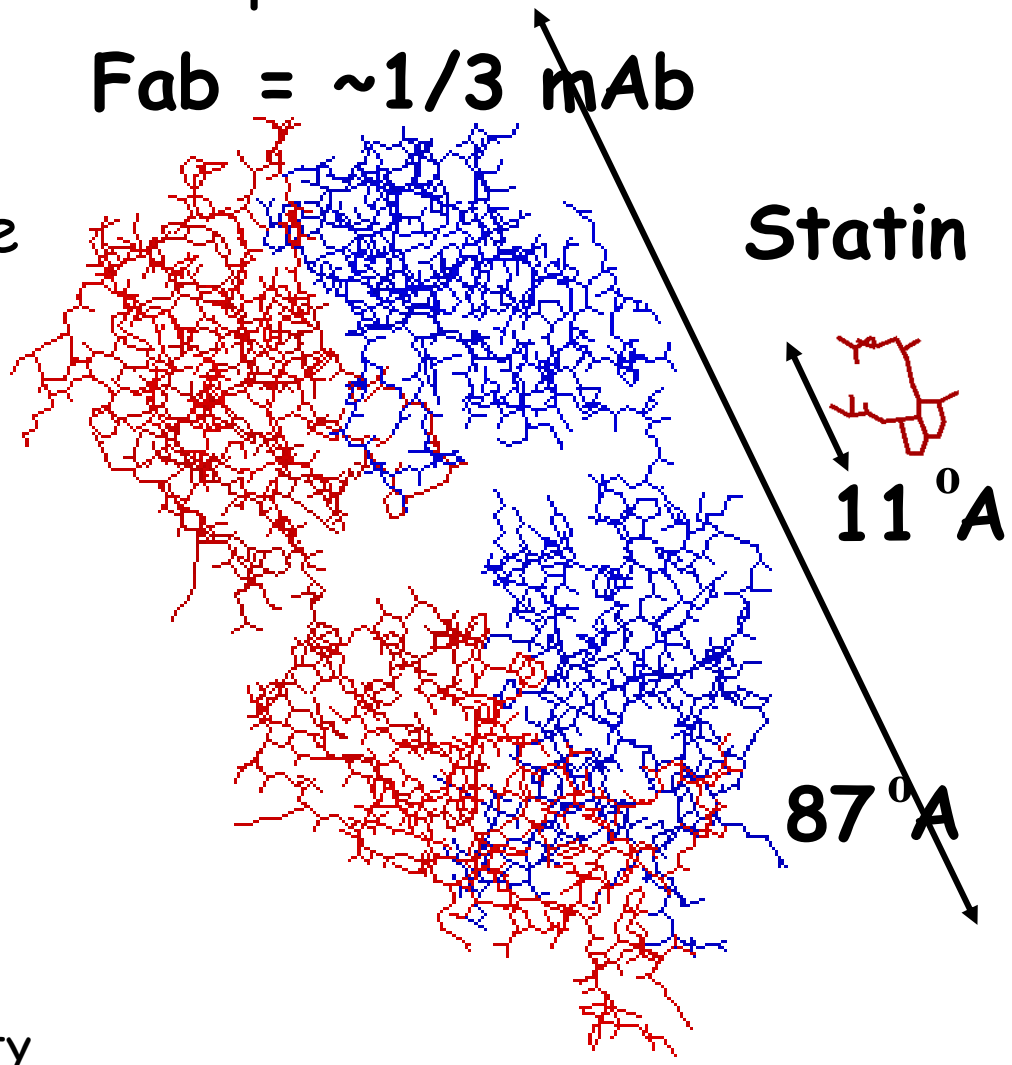
Chemistry Manufacture and Controls (CMC) Reviewer's Role

- Review of PreIND, IND, IDE, BLA, NDA includes:
  - manufacturing of the drug substance and drug product,
  - product characterization,
  - product control and product stability
  - mechanism of action
  - immunogenicity

Unique Attributes of Therapeutic Protein Products

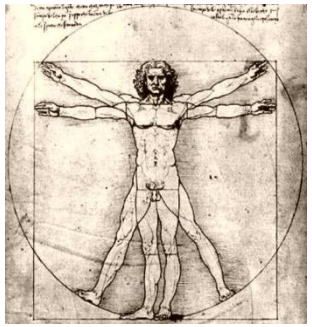
Biotech vs Small Molecule

- size and heterogeneity (glycoforms, PTM's)
- Higher order structure (primary-quatenary)
- complex manufacturing (living organisms, cell banks)
- impurities (process and Product related)
- Immunogenicity and Comparability



BIOTECH MANUFACTURING SYSTEMS

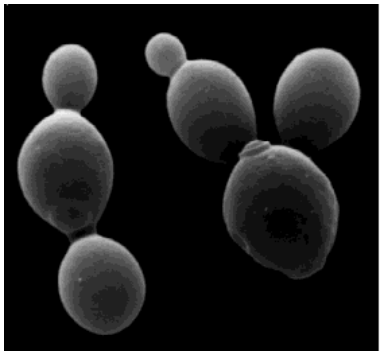
Mammalian and Insect Cell Culture



Potential for Adventitious Agents!!

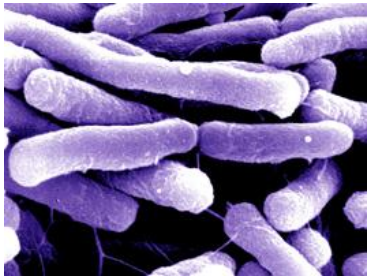
For instance bacteria, mycoplasma, fungi, viruses, and TSE)

Yeast



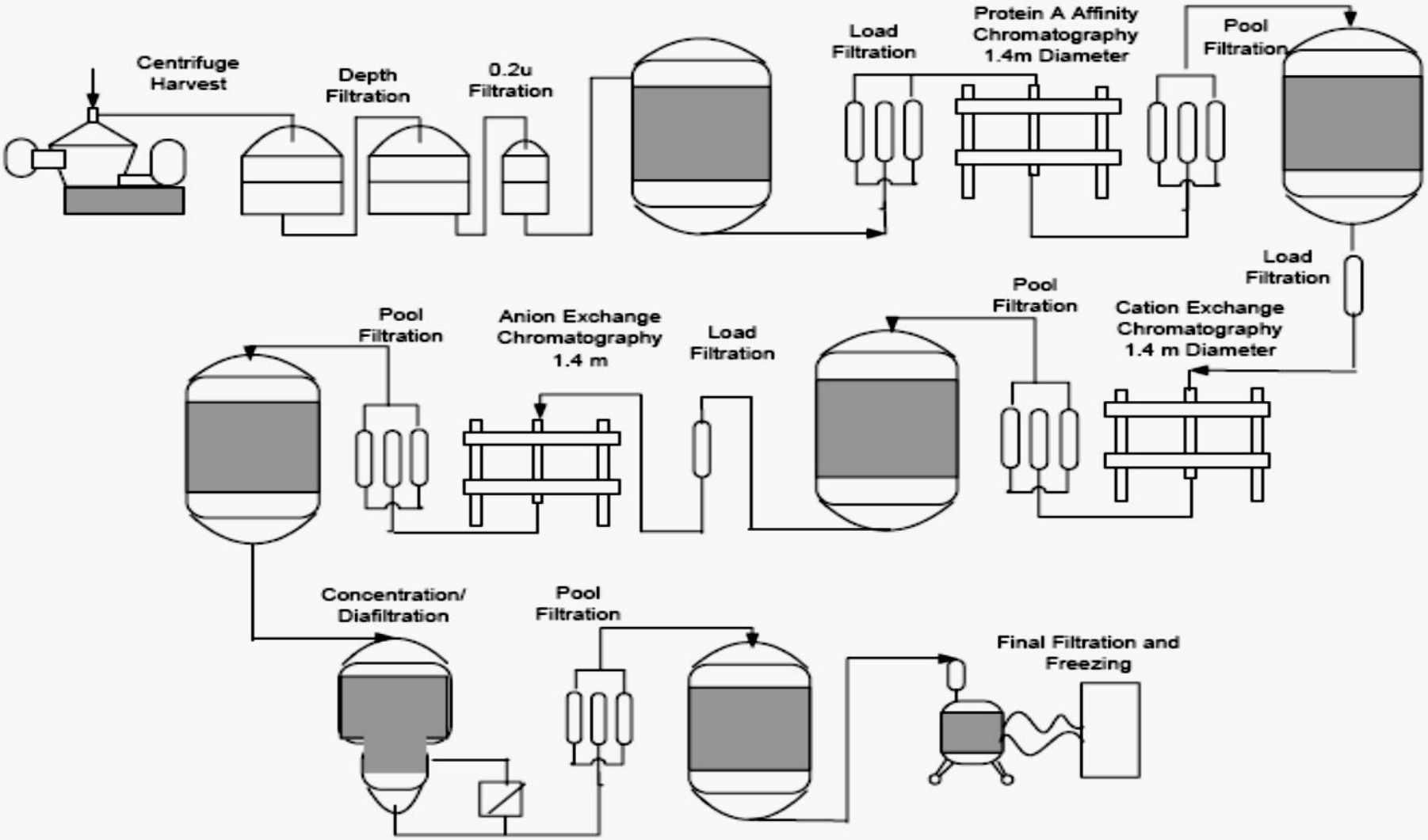
Carrot calli

Bacteria



Transgenic Plants and animals

Many unit operations with complex controls



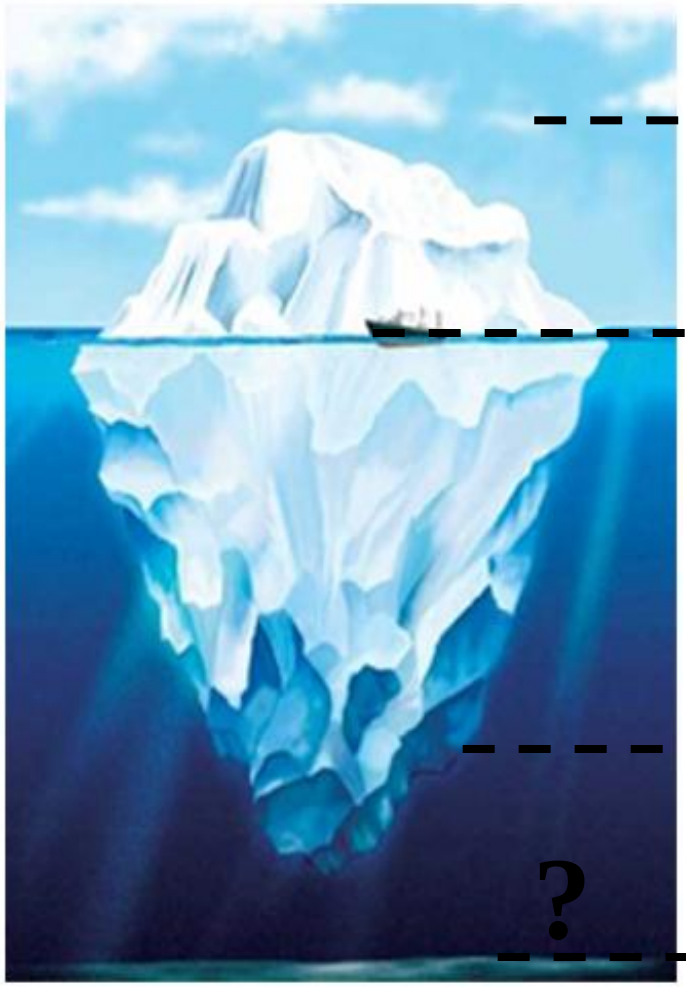
Things to Consider in Developing a Biotech Product

- Product characterization
  - Potency assays, impurities, stability
- Comparability
- Immunogenicity
- Communication with the FDA

Regulations

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.*

How Much of the Iceberg (desired product) Can We See?



- Release Tests
- Characterization
- Process

Product characterization

Product does not need to be fully characterized in order to begin clinical trials but…….

You should link drug substance and drug product lots from pre-clinical to early clinical (Phase 1/2) trials to the pivotal efficacy trial (Phase 3).

Product characterization

Develop sensitive and precise assays for characterizing the product as early in development as possible.

Why?

To support manufacturing changes

If changes to quality attributes occurs (e.g. new manufacturing facility, new container closure system); the more that is known about the quality attributes the better able one can assess the risk to the safety and efficacy of the product.

Example: Lysosomal Storage Enzymes (uptake and activity).

Potency Assays

PHS Act: 42USC262

(B) The Secretary shall approve a biologics license application - (i) on the basis of a demonstration that - (I) the biological product that is the subject of the application is **safe**, **pure**, and **potent**;

21CFR601.2

To obtain a biologics license …the manufacturer…shall submit data…which demonstrate that the manufactured product meets prescribed requirements of **safety**, **purity**, and **potency**…

(legal requirements)

Potency assays

Federal Food Drug and Cosmetics Act

SEC. 505. [21 U.S.C. 355] (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.
(b)(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application *(A) full reports of investigations which have been made to show whether or not such drug is* ***safe*** *for use* ***and*** *whether such drug is* ***effective*** *in use;*

What is potency?

21CFR600.3(s)

"The word potency is interpreted to mean the specific ability or capacity of the product (...) *to effect a given result*."

Linking Clinical Response to Potency

Clinical Response f Dose
Dose f Potency
$\therefore$ Clinical Response f Potency

This is why the potency assay should reflect the MOA whenever possible

Changes to potency = changes in clinical response

Bioassays for Therapeutic Proteins

The bioassay(s) should:

Reflect the *in vivo* mechanism(s) of action of the protein; sometimes more than one MOA

- Clotting factors: clot lysis and peptidolytic assays.
- Lysosomal storage enzymes: cellular uptake and enzymatic activity assays.

Impurities

- Develop methods to compare impurities in lots.

  Why? Knowing that an impurity has always been present throughout clinical development is knowledge you can leverage! Invest the time to understand your product's impurity profile.

- Determine if "impurities" are process- or product-related (Western blots, peptide mapping, ELISA for host cell proteins, *etc*).

- What do you know about the impurities? Do the impurities influence bioactivity, PK, toxicity, immunogenicity?

Knowing the Impurity Profile

Commercial vs Specific HCP Assays

	Host Cell Protein					
	Historical process Results				Current process Results	
Range	421 – 1256	290 – 644	154 – 303	83 – 146	39 – 123	47 – 76
Specific: Avg. ± Std. Dev.	933 ± 271	452 ± 112	207 ± 36	118 ± 18	78 ± 21	64 ± 10
Range	4 – 106	20 – 74	5 - 13	All ≤ LOQ[a]	All < LOQ	All < LOQ
Commercial: Avg. ± Std. Dev.	29 ± 25	49 ± 19	8 ± 2	All < LOQ	All < LOQ	All < LOQ

Develop a specific HCP assay early in development!

Stability
(things to consider)

- Need to ensure that product used in clinical trials is stable
  - ICH provides guidance on temperature and storage condition

- How stable is product under the conditions of use?
- Is the product compatible with the container closure system?

Most biotech drugs are stored in the cold. How would you maintain cold chain security and stability in a tropical country?

Comparability

- Biologic products undergo multiple manufacturing changes during clinical development and after approval.

- The goal is to demonstrate that pre and post change products are highly analytically comparable and that any observed differences are unlikely to impact clinical performance. Otherwise clinical or animal studies may be required.

- The more potential the manufacturing change has to alter critical quality attributes of the product the more comprehensive the physiochemical study should be.
    - Using irradiated serum vs change of filter

RETAINS, RETAINS, RETAINS

- Manufacturing changes are common in Biotech
- Should link critical quality attributes to those found in the clinical trial material
- Make sure retains are stable (-70°C)
- Also critical during analytical assay development
  -As technologies improve they may detect things not seen with older assays. Retains allow you to determine if they were always present.

Immunogenicity

- Can impact PK/PD, biodistribution, safety and efficacy
  - Safety Issues
    - Hypersensitivity
    - Neutralization of endogenous protein
    - Infusion related reactions
  - Efficacy Issues
    - Neutralization of the drug (blocks enzyme activity or receptor binding)
    - Change exposure – pharmacokinetics, biodistribution

Communication with the Agency

The Agency provides guidance during various types of meetings:

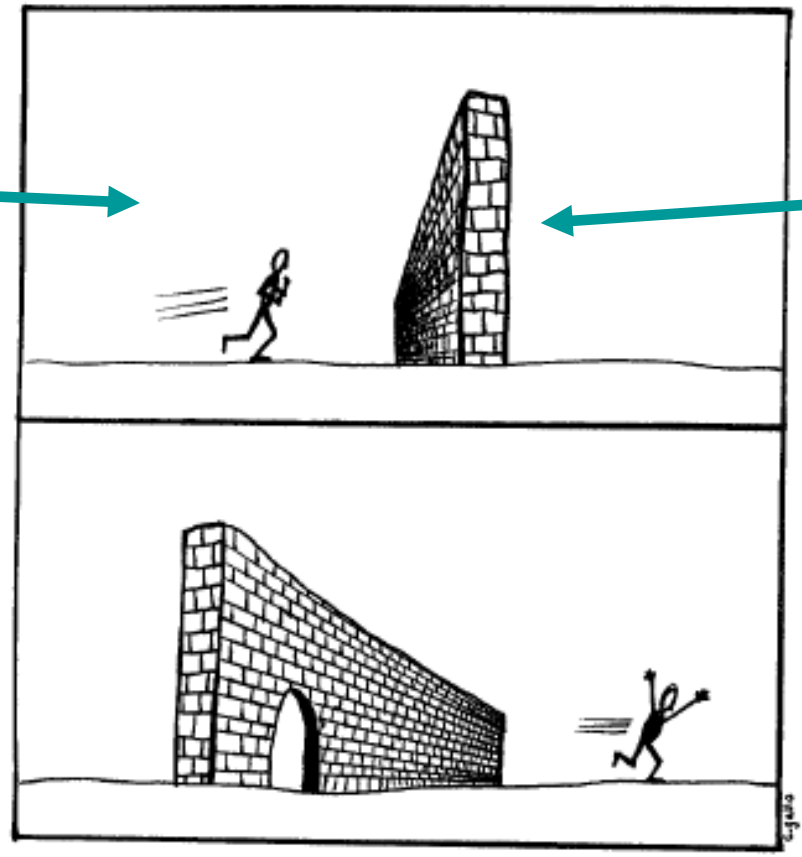
- Type A meeting: offer help with a stalled program development program.
- Type B meeting: pre-IND, Pre-BLA, Pre-NDA.
- Type C meeting: any other regardless of the development stage of the product. CMC only meetings are typically this type.

Also, see ICH guidelines, FDA Guidance for Industry and Points to Consider Documents

Phase I IND:
IT'S LIKE RUNNING INTO A WALL

SPONSOR

FDA



THERE IS A PATH FORWARD!

IND Application CMC Section for Therapeutic Proteins

- Expression System
- Cell Banks
- Manufacturing process
- Release specifications
- Stability data
- Container closure system
- Description of product
  - Mechanism of action if known
  - Characterization data
- Immunogenicity

We want to see data!!!

Descriptions and/or links to publications are not substitutes for a IND CMC section.

Safety issues are our biggest concern at phase 1.

Common IND Hold Issues For Therapeutics Proteins

- Lack of data on clearance of endogenous retrovirus
- Lack of appropriate specifications for critical tests (e.g.: sterility, endotoxin)
- Lack of basic product characterization
- Lack of potency assay or setting of appropriate specification limits
- Lack of information on product manufacturing
- Lack of information on human or animal derived materials
- Lack of stability data (as pertains to clinical trial)
- Lack of immunogenicity assay and/or reasonable qualification

CONCLUSIONS

- The greater the understanding of the products critical quality attributes and mechanism of the action the more effective your product development will be.

- Retains, retains, retains.

- Effective communication with FDA is recommended to reduce development time, cost and frustration

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Common Acronyms

- IND - Investigational New Drug
- BLA - Biological License Application
- NDA - New Drug Application
- ANDA – Abbreviated New Drug Application
- IDE - Investigational Device Evaluation
- PMA - PreMarket Approval Application (Device)
- PAS – Prior Approval Supplement
- CBE-30 – Changes Being Effective in 30 days
- CBE-0 – Changes Being Effective
- IPC – In-Process Controls
- IB – Investigator Brochure
- mAb – Monoclonal Antibody
- FDS – Formulated Drug Substance
- BDS – Bulk Drug Substance

Common Acronyms

- PHS Act - Public Health Service Act
- CMC - Chemistry Manufacturing Controls
- DS – Drug Substance
- DP – Drug Product
- ONDQA – Office of New Drugs Quality Assessment
- OND – Office of New Drugs
- DOE - Design of Experiments
- QbD – Quality by Design
- ICH - International Conference on Harmonization
- PK - Pharmacokinetics
- PD - Pharmacodynamics
- FD & C Act - Food, Drug and Cosmetic Act
- cGMP - current Good Manufacturing Practices
- GLP - Good Laboratory Practices
- SOP - Standard Operating Procedures

Common Acronyms

- IQ/OQ/PQ - Instrument Qualification/Operational Qualification/Performance Qualification
- CFR - Code of Federal Regulation
- PDUFA - Prescription Drug User Fee Act
- MDUFA - Medical Device and User Fee and Modernization Act
- HPLC - High Performance Liquid Chromatography
- SEC-HPLC - Size Exclusion Chromatography
- HIC - Hydrophobic Interaction Chromatography
- CEX - Cation Exchange Chromatography
- CZE - Capillary Zone Electrophoresis
- MS - Mass Spectrometry
- GC - Gas Chromatography
- FFF- Field Flow Fractionation
- AUC - Analytical Ultra Centrifugation or Area Under Curve

Common Acronyms

- SDS-PAGE - Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
- IEF - Isoelectric focusing
- MAPPs - Manual of Policies and Procedures
- WCB – Working Cell Bank
- MCB – Master Cell Bank
- EPC – End of Production Cells
- FDMA – Food and Drug Administration Modernization Act
- FDAAA – Food and Drug Administration Amendment Act
- PI - physician labeling or package insert
- IRB - Institutional Review Board
- CSO - Consumer Safety Officer
- RPM - Regulatory Project Manager
- USP – United States Pharmacopeia