CMC Considerations for Biotechnology Product Development: A Regulatory Perspective

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FDA SBIA Oncology Therapy Development Workshop: Pivotal Steps and Avoiding Pitfalls for Start-ups
March 30-31, 2021

Pharmaceutical Quality

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

The following presentation reflects the experiences of the presenters and should not be used in place of regulations, published FDA guidance or discussions with the Agency.

Outline

- Part 1: Know your product
  - Overview of the range OBP products
  - Review principles and development challenges
- Part 2: Communication is Key
  - Communication strategies and approach
  - Common product quality topics discussed with FDA
  - Case studies

Know YOUR product!

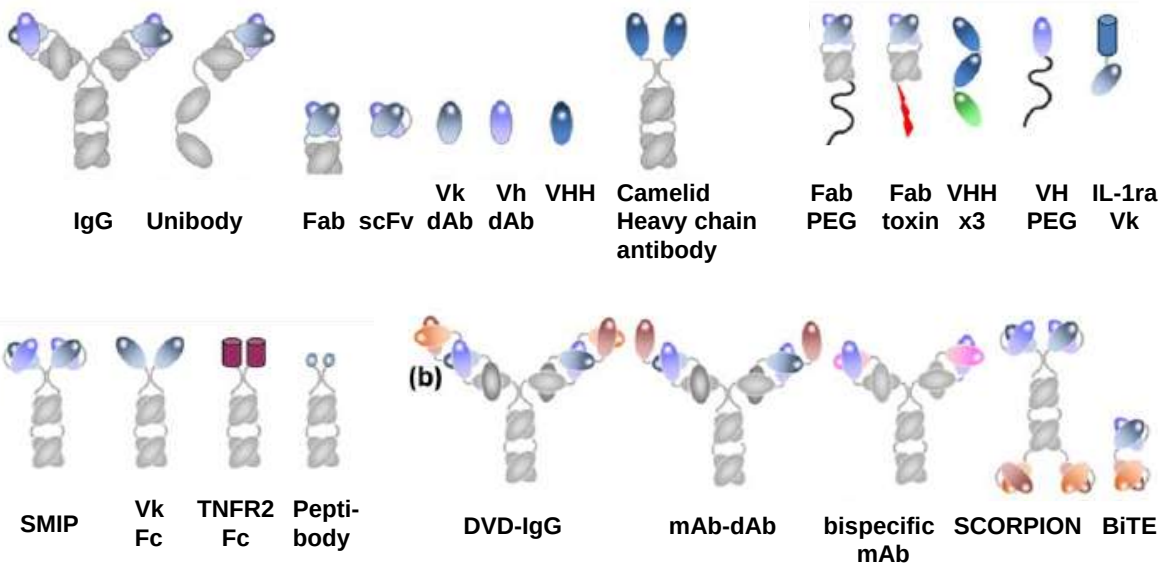
Wendy Weinberg, PhD

Current Laws governing regulation of biotechnology products

- **Public Health Service Act (1944)**
  - **Section 351- Licensure of biological establishments and products**
- **Federal Food, Drug, and Cosmetic (FD&C) Act (1938, 1962, 1997, 2007)**
  - **which interprets that "biological products" are also "drugs"**
- **Biologics Price Competition and Innovations Act of 2009**
  - **Part of the Patient Protection and Affordable Care Act**

Examples of biotechnology products reviewed in OBP

Antibody based



Non-Antibody based

Enzymes
Cytokines
Growth Factors
Soluble receptors
Bacterial toxins
Insulin

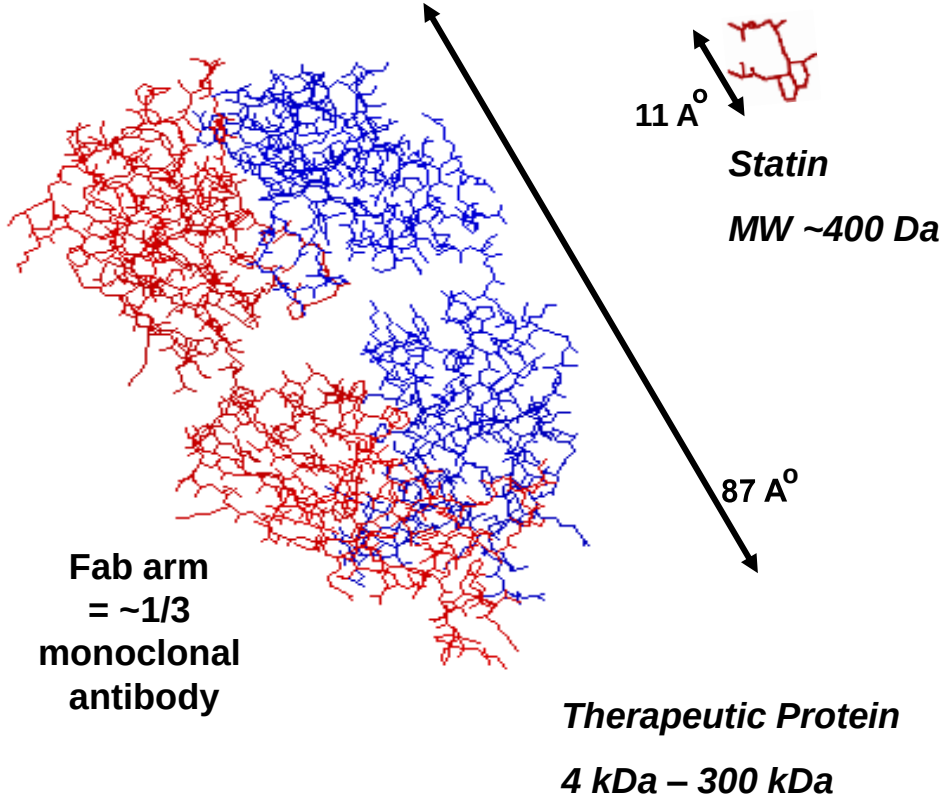
Modifications

Peptides
Enzymes
PEG
Radioisotopes
Drugs
Toxins

Adapted from: Enever et al, Current Opinion in Biotechnology 2009

Inherent challenges of biotechnology products

- Size
- Multiple levels of structure
- Multiple active sites, require proper conformation
- Post-translational modifications
- Heterogenous
- Susceptible to multiple degradative pathways



Product quality review principles for biotechnology products

- **Product quality is controlled by:**
  - Structure/function understanding
  - Physico-chemical characterization
  - Bioassay reflecting mechanism(s) of action
  - Established release specifications
  - Manufacturing process control
  - Demonstration of comparability following manufacturing changes

Biologic Review Principles
Ensuring safety, purity, and potency

Major areas of focus:

- **Product characterization**
- **Manufacturing process**
- **Comparability**

Heterogeneity: an inherent characteristic of biotechnology products

Examples of analytical approaches for product characterization:

- **Size, aggregates, charge, hydrophobicity**:
  - Chromatography resins; gel & capillary electrophoresis, light scatter, IM-MS, Analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, light scatter, microscopy
- **Glycosylation**
  - Anion exchange, enzymatic digestion, peptide mapping, CE, MS
- **Bioactivity**
  - Cellular and animal bioassays; ligand & receptor binding (ELISA, surface plasmon resonance), signal transduction

The assays selected should be suitable for the specific product attributes

Measuring Biological Activity (ICH Q6B)

- The specific ability or capacity of the product *to achieve a defined biological effect*
- The quantitative measure of biological activity is the product's potency
- The results of bioassays should be expressed in units of activity calibrated against a reference material run in the same assay
- Required under the Public Health Service Act

Bioassay as an indicator of clinical efficacy

- A well-designed bioassay reflects the mechanism(s) of action of the product
- Multiple mechanisms are likely:
  - Identify subset of mechanisms that impact safety and efficacy for intended indication; more than one assay may be required
  - The same product may have different bioassays for different indications

Examples:

- Cell-based assay
  - Primary cells
  - Clonal cell lines
  - Recombinant cell lines
- Binding assays
- Enzyme activity assays
- *in vivo* animal assay

Product-Related Variants

- **Product-related substances** - have properties comparable to those of the desired product with respect to activity, efficacy and safety

- **Product-related impurities** – arise during manufacturing or storage and are uncharacterized or do not have properties comparable to the desired product with respect to activity, efficacy and safety

Control by in-process or release testing

Product Knowledge and Control:

Adequacy of Methods to Detect and Quantitate Specific Product Attributes

- Are the tests capable of detecting modifications that might occur in the product?
- Are they capable of detecting all impurities that might occur?

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Manufacturing: Defining the process

- Molecular Expression Construct
- Expression system/Cell substrate
- Upstream production
  - Cell expansion, production culture, harvest
- Downstream production
  - Multiple purification steps
    Chromatography:
    affinity, ion exchange, hydrophobic interaction, size exclusion
  - Virus reduction steps
- Formulation
- Facility inspection prior to licensure; post-approval

Manufacturing:

Process-related impurities (PRI)

Examples:

- **Media components (insulin, transferrin)**
- **Chemical additives (antibiotics, inducers)**
- **Cell components (Host cell proteins, DNA)**
- **Contaminants (Adventitious & endotoxin)**
- **Leachables (Protein A, resins, heavy metals)**

Manufacturing control strategies

- Control of raw materials
- Use of chemically defined reagents for culture media
- Establish Master Cell Bank/Working Cell Bank
  - Qualified to be free of contaminating microbes, adventitious viruses
- Safety testing of End-of-Production cells and unprocessed bulk harvest
- Viral clearance studies
- In-process control testing for process- and product-related impurities
- Microbial control throughout the process
- Adequate cleaning of reusable components or use of disposable systems

Issues can arise at any stage of the manufacturing process

Selected examples:

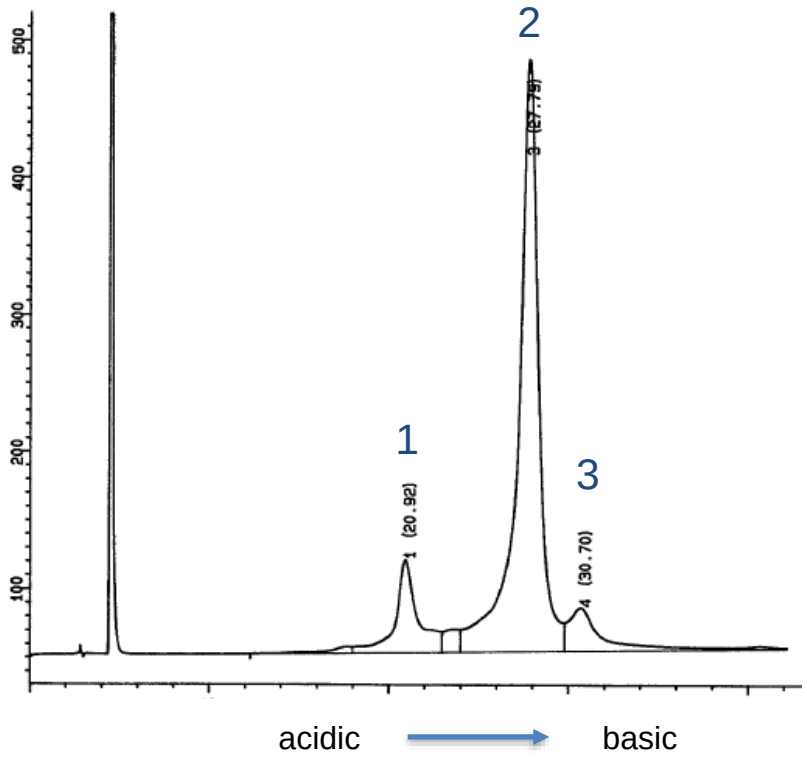
- Development of producer cell line:
  - Lack of clonality leads to new product variants
- Upstream (culture process), change in medium components:
  - Altered producer cell growth characteristics
  - Altered post-translational modifications
- Downstream (purification):
  - Co-purified proteins
  - Co-purified host cell protease, product degradation
- Formulation:
  - Aggregation/Precipitation

Lot Release Specifications:
Drug Substance and Drug Product

- Allows continuous monitoring of product quality
- Ensures levels of critical attributes maintained, restricts presence of impurities
- Established acceptance criteria for product- and process-related impurities
- Quantitative acceptance criteria are established at Phase 1 and are progressively refined as product development proceeds

Setting Specifications based on Product Knowledge

Purity by charge heterogeneity: Ion exchange chromatography



Set acceptance criteria based on:

- Product characteristics
- Manufacturing capability
- Assay capability

Peak	1	2	3
Bioactivity	98% RS	120% RS	30% RS
Specification		% area ≥70.0%	% area ≤20.0%

Protein Product Stability

Susceptible to multiple stability failures, *e.g.*:

- Aggregation, precipitation
- Proteolysis
- Unfolding
- Oxidation
- Deamidation
- Adduct formation

→ *Identify assays to detect pathway of degradation*

→ *Establish stability protocol*

Biologic Review Principles
Ensuring safety, purity, and potency

Major areas of focus:

- **Product characterization**
- **Manufacturing process**
- **Comparability**

Comparability Assessments:

To ensure consistency of product following significant manufacturing changes, *e.g.*:

- Change in critical reagents
- Scale-up in production
- New facility

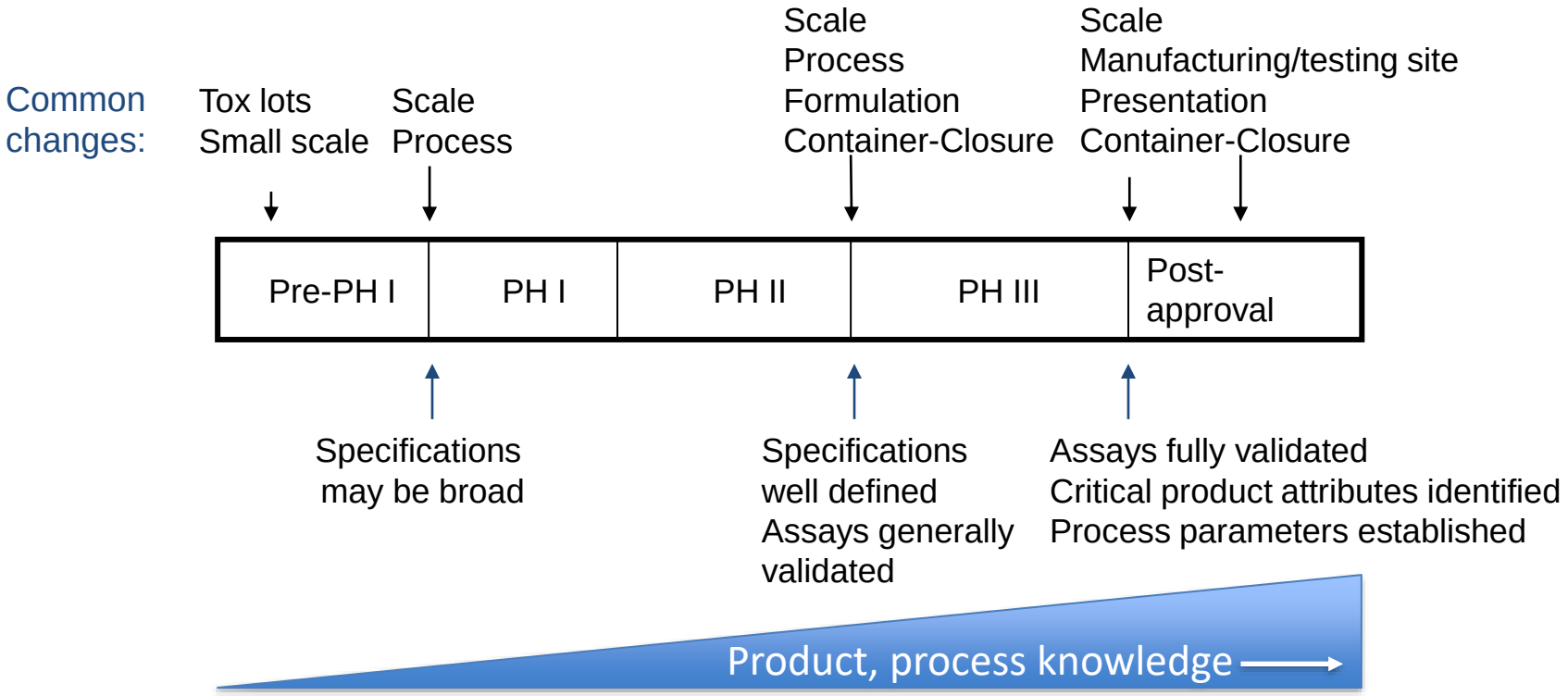
Comparability Assessments:

- Analytical studies:
  - Release tests
  - Additional characterization studies
  - Side-by-side comparative analyses
  - Co-mixture analyses
  - Relevant in-process assays
  - Trending
  - Stability (real-time, accelerated, stressed)
- Animal testing
- Clinical study
- Relative to stage of clinical development

Relating Product Quality to Safety and Efficacy

- Manufacturing changes may result in unanticipated product-related variants - clinical impact unknown.
- It’s important to know the range of modifications for which there is clinical experience.
- The more you know about the critical parameters in the manufacturing process, the better you can predict the potential impact of changes on the product.
- The more knowledge you have on the critical quality attributes of your product, and the better your assays, the better you can predict the clinical impact of those differences.

Product knowledge increases throughout product lifecycle



Review principles: Take home messages

- **Biotechnology products are heterogenous mixes**
- **Goal is to ensure consistent, safe, pure and potent product**
- **This is achieved by control of the manufacturing process and through product quality release testing**
- **It is important to identify critical quality attributes and to establish optimal testing strategies for specific protein characteristics**
- **Each product is different; evaluated as part of overall control strategy**

KNOW YOUR PRODUCT – CONTROL YOUR PROCESS

Useful quality resources for biotechnology products

FDA Points to Consider:

- Points to consider in the manufacture and testing of monoclonal antibodies for human use
  https://www.fda.gov/media/76798/download
- Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals
  https://www.fda.gov/media/70868/download

FDA 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
- For the submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use

International Conference on Harmonization (www.ich.org):

- ICH Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin (Sept. 1998)
- ICH Q5C: Stability Testing of Biotechnological/Biological Products (July 1996)
- ICH Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products (Sept. 1998)
- ICHQ5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process
- ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Aug. 1999)