Quality Attributes of Biologics and Biologic Standards

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USP and *NF* Are Official Compendia

USP Is Cited in Law…

- **1848:** Drug Import Act
- **1906:** Pure Food and Drug Act
- **1938:** Federal Food, Drug and Cosmetic Act
  - Definition of a drug, Adulteration, Misbranding and Drug product name
- **1994:** Dietary Supplement Health and Education Act
- **2003:** Model Guidelines for Medicare Formularies

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Role of Compendial Standards

- Provide independent assessment of identity, quality, strength, and purity of therapeutics
- Allow verification by 3rd party laboratories (Industry, QC labs, Regulatory Agencies)
- Integrate harmonized testing into a public standard so that safety and quality are preserved
- Scope of testing from production to consumption

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Boundary Assumption

USP standards are a critical, but by no means all-comprehensive set of parameters that describe attributes and quality of an article in commerce, they can potentially be a helpful resource of relevance to regulatory licensing decision making, but are not intended for that purpose, hence:

A USP monograph under the same title may describe multiple articles in commerce that differ in specific aspects of their licensed attributes that are not covered in the monograph

i.e., FDA may prescribe additional standards that are material to an article's "sameness"

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Quality Control for Biotechnology Products - ICH

ICH Guideline Q6B - Test Procedure and Acceptance Criteria for Biotechnology/ Biologic Products

- Quality Attributes
  - Identity
  - Purity
  - Impurity profile
  - Potency
  - Strength
  - Safety

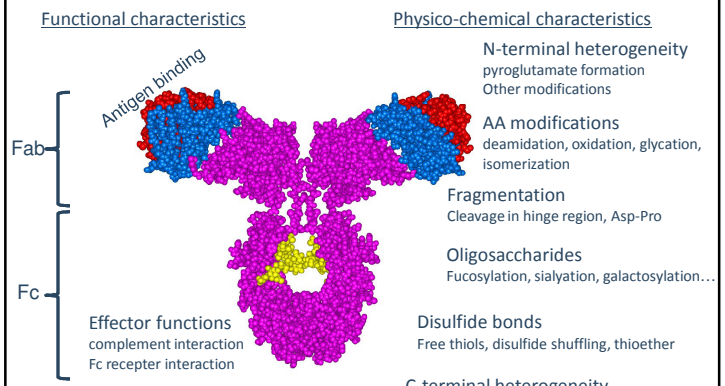
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Critical Quality Attributes of Biotechnology Products

- Each quality attribute is evaluated for criticality using a risk ranking approach (per ICH Q9), which assesses the possible impact of each attribute on safety and efficacy.
  - Process related impurities (host cell DNA and proteins, endotoxins, reagents and ancillary materials)
  - Process contaminants (leachables, adventitious agents)
  - Potential for a variety of tertiary and quaternary structures, with a lack of validated methods to measure 3-D structures and 3-D population profiles (Bioassay)
  - Product-related variants - **Each modification of a Biomolecule can be described as a "Quality Attribute".**

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Quality Attributes to Consider - Mab



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Possible Modifications to Recombinant Therapeutics

- **Chemical**
  - Deamidation, Isomerization, Oxidation, Disulfide Scrambling
- **Translational**
  - Misincorporation, Reading frame shift, Intron read throughs
- **Post-translational**
  - N- and O- Linked glycosylation, Phosphorylation
- **Enzymatic**
  - Proteolytic clipping
- **Physical**
  - Denaturation, Non-covalent aggregation

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Tools and methods for analyzing the various product attributes are well established

Molecular Parameter	Attribute	Methods for control and characterization
Primary structure	Sum formula: Mass of light chain, heavy chain and of intact mAb	LC-ESI-MS
	Amino acid sequence	Orthogonal peptide maps with high resolution MS and MS/MS sequencing
	Disulfide bridging	Non-reducing Peptide Map
	Free cysteines	Ellman's, Peptide Map
	Thioether bridging	Peptide map, SDS-PAGE, CGE
Higher order structure	Secondary and tertiary structure	CD spectroscopy, DSC, H-D-Exchange, FT-IR
Glycosylation	Glycan isoforms	NP-HPLC-ESI-MS of 2AB-labeled glycans, exoglycosidase digestion, MALDI TOF/TOF
	Sialic Acids incl. NGNA	NP-HPLC, WAX, HPAEC; RP-HPLC (DMB-label)
	Aglycosylated mAb	CGE, Peptide map
Heterogeneity	C- and N-terminal: ±Lys, pyroGlu	CEX; Papain-IEX; Peptide Map, RP-HPLC
	Glycation of Lys	Boronate affinity; LCMS; Peptide map
	Oxidation	RP-HPLC; Papain-HIC; Peptide map
	Deamidation	CEX; Papain-IEX; Peptide map
	Aggregation	SEC, FFF, MALLS, DLS, AUC; imaging, particle char.
	Fragmentation at disulfides (HL, H_2L, H, L) and in amino acid chain (p100, p50)	CGE, SDS-PAGE, SEC, RP-HPLC

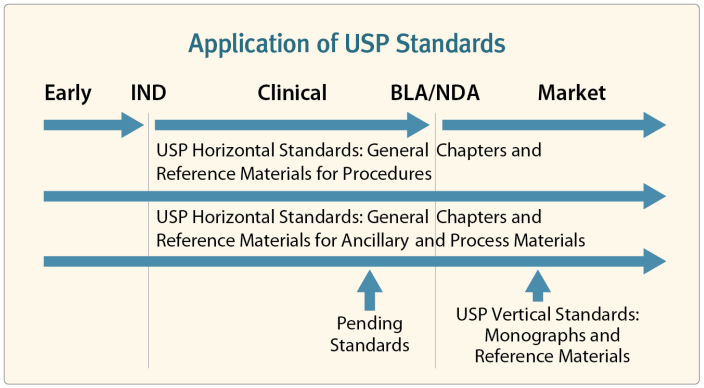
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Increasing Access/Affordability

- Biologics are expensive and often difficult to manufacture, *but they can offer massive public health benefits*
- Making them as widely available as possible is a key public health goal - **Affordable price**
- Multiple Products are coming into the market
- Global standards are vital
  - Maintain high quality of the products in a global market

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USP Standards—Biological Medicines



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USP B&B Expert Committees and Expert Panels

General Chapters Biological Analysis	Monographs 1	Monographs 2
Glycoprotein & Glycan Analysis	Glucagon	Epoetin*	Tissue and Tissue-Based Products	Plasma Protein Analytical
<30> Residual DNA Testing			
<1050.1> Viral Clearance	Pharmaceutical Enzyme Preparations	Unfractionated Heparin	Coagulation Factors*	CD34 Positive Cells
<1106> Immunogenicity			
<57> Protein Determination Procedures	Low Molecular Weight Heparins	Insulin		
<1239> Viral Vaccines			
Residual Host Cell Proteins	Therapeutic Peptides			
Recombinant Therapeutic MAbs				
Vaccine Poly-saccharide NMR Identity Testing				

* These panels are no longer active and will be retired soon.

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2010-2015 Council of Experts - Demographics

- 1028 experts serving on 26 Expert Committees, 72 Expert Panels and 1 Advisory Group
- 421 Expert Committee members
- 448 Expert Panel members
- 28 Advisory Group members
- 131 Government Liaisons
- 282 (32%) international experts from 48 countries:
  42 from India, second to USA

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Capturing Platform Assays in a Compendial Chapter

- *<129> Analytical Procedures for Recombinant Therapeutic Monoclonal Antibodies*
  - Will contain a collection of validated compendial procedures with established system suitability criteria for therapeutic MAbs
    - Size Exclusion Chromatography (SEC)
    - Capillary SDS Electrophoresis (reduced and non-reduced)
    - Oligosaccharide Analysis (N-Glycan analysis)
    - Sialic Acid Analysis

  Will be accompanied by USP MAb System Suitability RS

  Will not contain product or class specific acceptance criteria

  Will be supported by multiple >1000 Information Chapters that discuss quality attributes, manufacturing and quality control aspects for MAbs

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Quality Control Assays for mAbs

- Other USP chapters
  - Content :<1057> Total Protein Measurement
  - <1055> Biotechnology-Derived Articles—Peptide Mapping
  - Process Related Impurity assays
    - <1132> Residual Host Cell Protein Measurement in Biopharmaceuticals
    - <1130> Residual DNA Testing
    - Protein A
  - <791> pH
  - <71> Sterility Tests

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Filgrastim Drug Substance Monograph

- **Definition:**
  - "It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escheria coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor. When prepared as a drug substance, it contains NLT 1.0 mg/mL of Filgrastim…it has a biological potency of NLT 80% and NMT 125% relative to the standard."
- **Identity**
  - Bioassay
  - Chromatographic profile
  - Peptide map
- **Assay (Potency)** - Bioassay
- **Impurities**
  - Product related by RP HPLC
  - Total impurities by SDS-PAGE & High Mol.Wt by SEC-HPLC
  - Charge variants by IEF
- **Specific Test –** Protein Conc. by RP-HPLC

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USP Bioassay Chapters

Official since 1950:

- <111>: *Design and Analysis of Biological Assays*
  - A major revision will be proposed in *Pharmacopeial Forum PF39(4)*

The new suite:

- <1030>: *Biological Assay Chapters – Overview and Glossary*
- <1032>: *Design and Development of Biological Assays*
- <1033>: *Validation of Biological Assays*
- <1034>: *Analysis of Biological Assays*

All of these chapters are focused on relative potency bioassays.

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Summary

- A pharmacopeial monograph captures the key quality attributes of a medicinal product in terms of identity, strength and purity.
- For biological medicines key quality attributes are often more difficult to define and require multiple, orthogonal tests.
- A pharmacopeial monograph is able to accommodate complex and multi-manufacturer products, also for biologics and biotechnology-derived articles – flexible monograph approach can be considered.

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UPS-India Biology Laboratory Capabilities

- Analytical Method Development:
  - ***Identity, purity,, safety, Impurity profiling, forced degradation studies, and cell-based potency assays***
- Validation of analytical methods
- Cell-Biology:
  - *Cell line generation, banking and distribution*
- ELISA- based assays for vaccines and immunogenicity testing
- Viral assays
- Reference Standard establishment
- Stability testing
- Protein characterization
- Sterility & Endotoxin testing
- Microbial identification
- Anti-microbial Efficacy testing

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Education and Training programs conducted by USP-India

Hands On Training-

- Method Development & Validation for Bio Pharmaceuticals
- Bioassay design, Development & Validation
- Bacterial Endotoxin Testing

Class Room Training -

- Analysis of Biopharmaceuticals
- Essentials of Microbiological Testing
- Rapid Microbiology

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Call for Candidates: 2015-2020 Council of Experts

- **Global Expertise, Trusted Standards, Improved Health**
  - Utilize Your Expertise
  - Advance Your Profession
  - Improve Drug and Food Quality
  - Improve Public Health
- **Seeking experts in pharmaceutical, biological, and food sciences; pharmacy; medicine; and related disciplines to volunteer for USP's Council of Experts and Expert Committees for the 2015-2020 cycle**
- **Contact USPVolunteers@usp.org to receive related email announcements, including next cycle's expert committee structure and the official launch (Fall 2013) of the Call for Candidates**

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Thank You

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