



U.S. PHARMACOPEIA  
*The Standard of Quality<sup>SM</sup>*

# **Biosimilar/Follow-On Biological Products – USP Perspective**

Tina S. Morris, Ph.D.  
Director, Biologics & Biotechnology  
United States Pharmacopeia

**Biosimilars Today**  
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## Summary

- ◆ Public monographs and national primary reference materials—a government responsibility that came to USP historically
- ◆ ‘Sameness’ questions require special types of standards—USP is good at standards
- ◆ Open public dialogue and debate are critical
- ◆ Public standards are key to maintaining unitage within and across products
- ◆ This is critical to practitioners to understand dosing and switching
- ◆ USP is a practitioner-based compendium—the only one in the world: we’re here to help



# An 1820 USP Monograph

## TINCTURES.

### TINCTURE OF OPIUM. CALLED LAUDANUM.

Take of Opium powdered, two ounces.  
Diluted alcohol, two pints.  
Digest for ten days, and filter.

### TINCTURE OF QUASSIA.

Take of Quassia rasped, one ounce.  
Diluted alcohol, two pints.  
Digest for ten days, and filter.

### TINCTURE OF RHUBARB.

Take of Rhubarb bruised, three ounces.  
Diluted alcohol, half an ounce.  
Digest for ten days, and filter.



## 1938 FDC Act : Section 501 (b) - Adulteration

- ◆ A drug or device shall be deemed to be adulterated if it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium.
- ◆ Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium...



## The Act (continued)

- ◆ except that whenever tests or methods of assay have not been prescribed in such compendium, or such tests or methods or assay as are prescribed are, in the judgment of the Secretary, insufficient for the making of such determination, the Secretary shall bring such fact to the attention of the appropriate body **[that's USP!]** charged with revision of such compendium, and if such body fails within a reasonable time to prescribe tests or methods of assay which, in the judgment of the Secretary, are sufficient for purposes of this paragraph, then the Secretary shall promulgate regulations prescribing appropriate tests or methods of assay in accordance with which such determination as to strength, quality or purity shall be made.
- ◆ **A historic public/private partnership that works today**



## Provisions of the FDCA apply to biologics regulated under PHS Act

- ◆ PHS ACT (42 USC 262)
  - ▶ 262(j) Application of FDCA:
    - *The Federal Food, Drug, and Cosmetic Act... applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act (21 U.S.C. 355)*
- ◆ **Biological products approved under the PHS Act are subject to the adulteration and misbranding provisions of FDCA**
- ◆ **If an official monograph in USP-NF is available, the biological product, *including a generic biologic*, should conform**



## USP and Biologics

- ◆ 1985 - Convention Resolution 'Feasibility and Advisability of Compendial Monographs for Macromolecular Drugs Derived from Biotechnological Processes'
- ◆ 1987 - USP Biotechnology Program
- ◆ 1990 - Proposed monographs on Alteplase, Interferons, Somatrem, and Somatropin
  - ▶ Biologics and Biotechnology related general chapters in USP
- ◆ 1992 - PF 'USP Rationale for Development of Public Standards for Biological Products Licensed by CBER'
- ◆ 1995 - USP Subcommittee on Biotechnology and Biopolymers



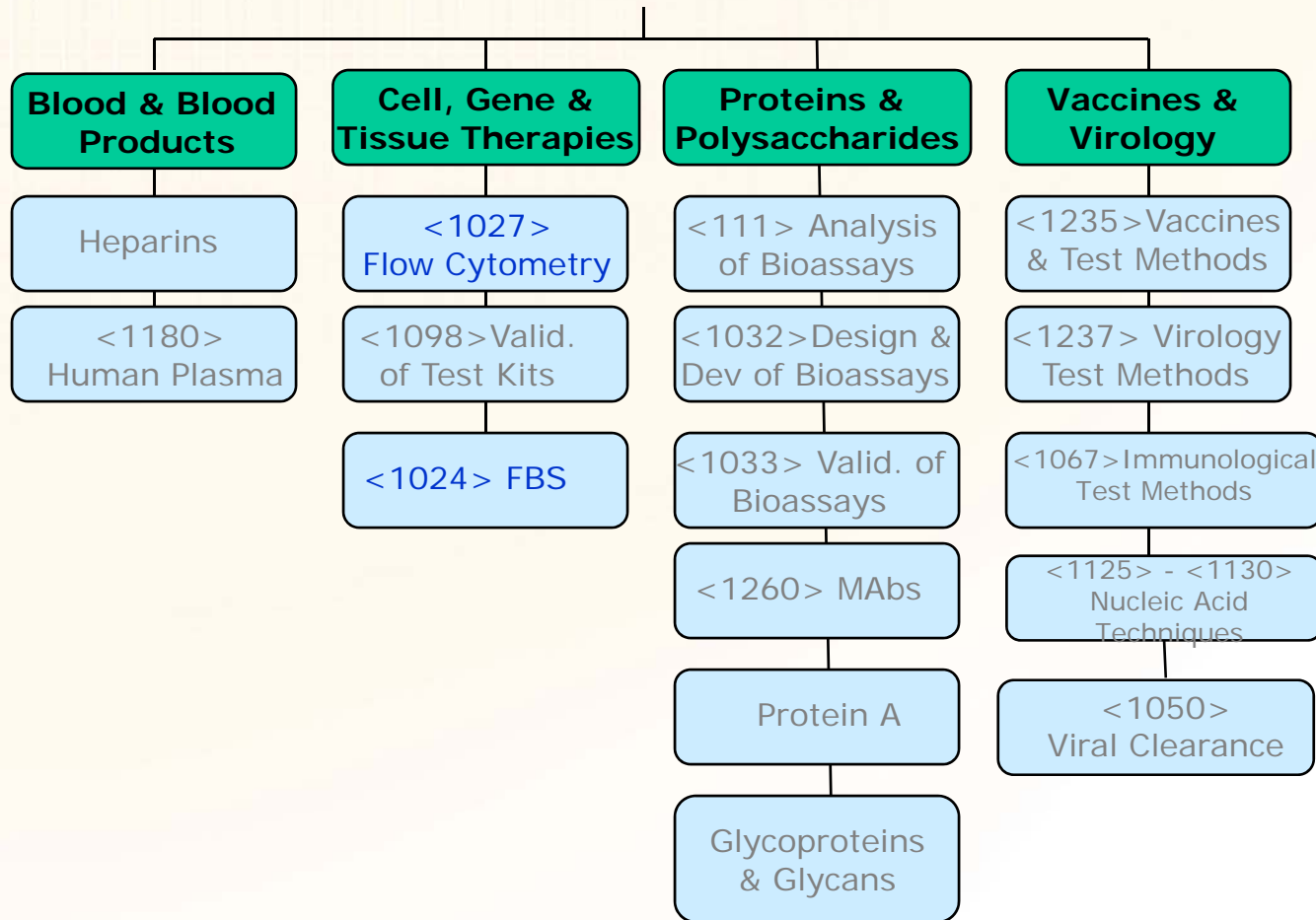
## Resolution 2—2000 USP Convention

- ◆ *Explore the Feasibility and Advisability of Developing Guidance on Principles and Approaches to Assure Equivalence of Complex Active Ingredients (Including Botanicals and Dietary Supplements), Recognizing the Special Issues Associated With Agents of Biologic/Biotechnological Origin Including Their Regulatory Control. Initiatives Should Be Undertaken in Collaboration With Appropriate Partners*



# USP: a Scientific Resource

## Biologics & Biotechnology Collaborative Group



4  
Committees

16 advisory  
panels



## US Congress: Access to Life-Saving Medicines Act: Creates a Biologics Generic Pathway (Proposed)

- ◆ Amends Public Health Service Act
- ◆ Adds abbreviated application for 'biosimilar' biologic product
- ◆ Test: Comparator Biological Product (CBP)
- ◆ Reference: Reference product (RP)
- ◆ Biosimilar--'Absence of Clinically Meaningful Differences' between RP and CBP
- ◆ Requires 'thorough characterization'
- ◆ Allows 'interchangeability' studies—RP and CPB



# Principal Molecular Structural Features

- ◆ Non-glycosylated] proteins--differences allowed in translation, transcription, and post-translation, to include 'minor' differences in amino acid sequence
- ◆ Polysaccharides with similar repeating units, different number of units, and post-polymerization modifications
- ◆ Glycosylated protein as for non-glycosylated proteins and polysaccharide differences
- ◆ Nucleotides requires identicality
- ◆ Live viruses-- may be comparable

BUT: if not above, then not 'pharmaceutically equivalent' and not comparable



# 'Difference' and 'Sameness' Questions

- ◆ New Drug Safety and Efficacy (Different)
  - ▶ Null hypothesis of no difference versus alternative hypothesis of difference—rejection of Null means efficacy
- ◆ Comparable/Interchangeable (Equivalent)
  - ▶ Null hypothesis of inequivalence versus alternative hypothesis of equivalence—rejection of Null means equivalence
- ◆ Equivalence
  - ▶ Considers whether results of comparison are sufficiently similar
  - ▶ Requires criterion, goalposts (equivalence interval), and statistical test



## Proposed Law

- ◆ **Biosimilarity (comparability) and interchangeability are equivalence questions and require standards**
- ◆ **The first is a lesser standard; the second is a greater standard**
- ◆ **How does one make a lesser standard?**
  - ▶ **Reduced number of tests, types of tests, average criterion, widen goalposts, other**
- ◆ **How does one make a greater standard?**
  - ▶ **Increased number and types of tests, narrow goalposts, individual criterion)**



# Existing Comparability Approach within the Product Life Cycle

- ◆ Provides a linkage between the clinical and commercial stage process/product
  
- ◆ Testing may include comparison of:
  - ▶ cell culture process parameters
  - ▶ purification process parameters
  - ▶ biochemical characterization
  - ▶ animal PK studies
  - ▶ human PK studies



# Marketplace Impact

## ◆ Biosimilarity (Comparability)

- ▶ MD switches (? Formulary)
- ▶ May require detailing
- ▶ Less intense price competition

## ◆ Interchangeability

- ▶ Payor/pharmacist can switch
- ▶ No detailing
- ▶ More intense price competition

## ◆ Growth Hormone

- ▶ Genotropin
- ▶ Humatrope
- ▶ Norditropin
- ▶ Nutropin
- ▶ Saizen
- ▶ Omnitrope
- ▶ Others



## What is the role of a functional bioassay?

*To develop any biological therapeutic agent successfully, it is necessary to characterize the product thoroughly, both physicochemically and biologically. . . . .  
.. The biological activity or potency of the product must be appropriately assessed through a functional assay unless specifically justified otherwise, e.g., for binding proteins where binding has been correlated with biological activity. . . .*

From A.R. Mire-Sluis, Developments in Biologicals (Basel, Switzerland), (2002), Vol. 107 (Design and Analysis of Potency Assays for Biotechnology Products), pages 107 - 115

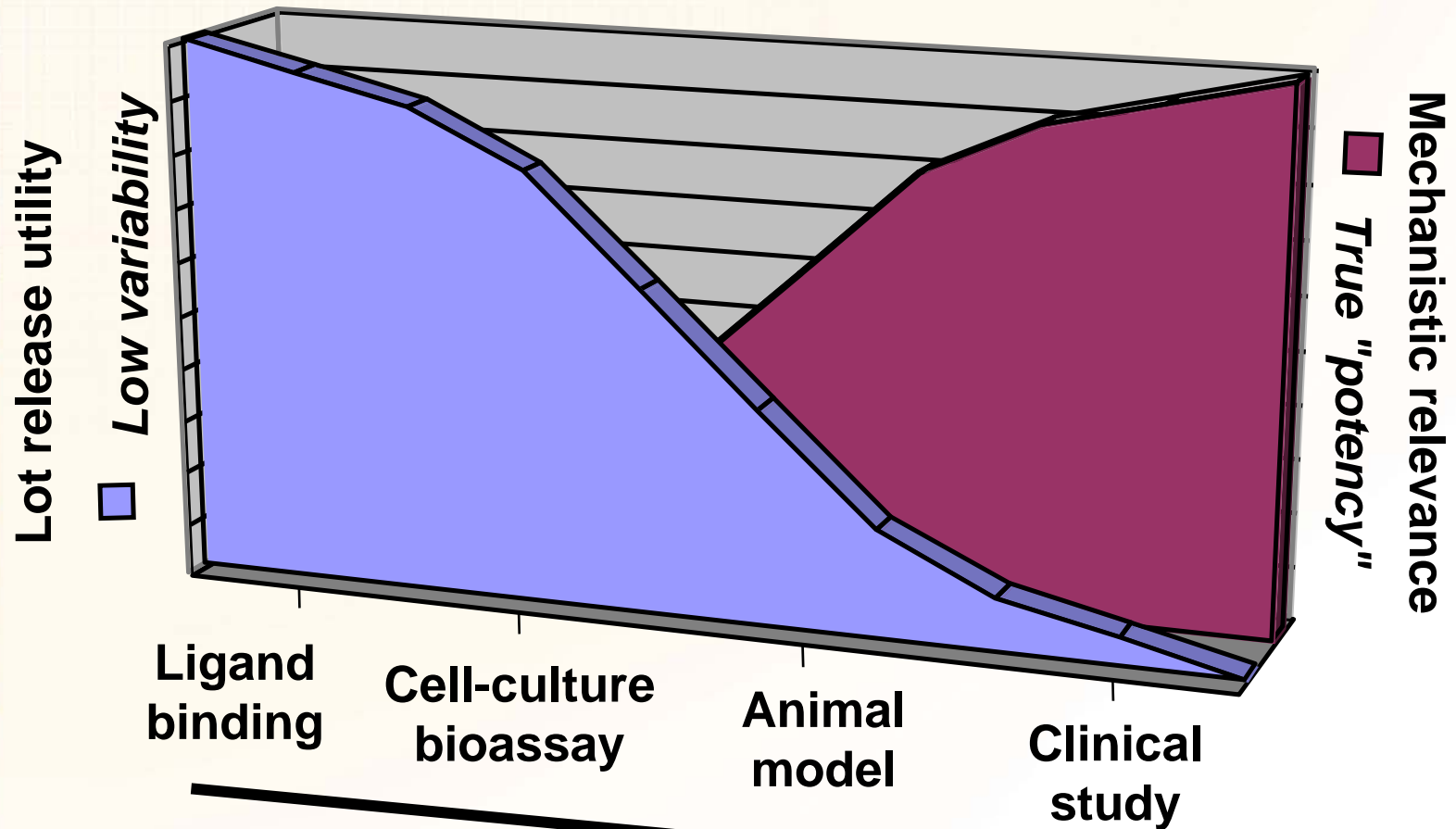


## When Are Bioassays Needed in a Monograph

- ◆ Bioassays are a probe of the 3-D conformation or a method for measuring the potency of complex products where activity may be attributable to more than one component
- ◆ EP and USP Differ
  - ▶ Somatropin (Bioidentity Test)
    - EP: No Bioassay
    - USP: Rat weight gain assay
  - ▶ Insulin (Bioidentity Test)
    - EP: No Bioassay
    - USP: Rabbit blood glucose



# Bioassay Continuum



Steven Kozlowski, US FDA



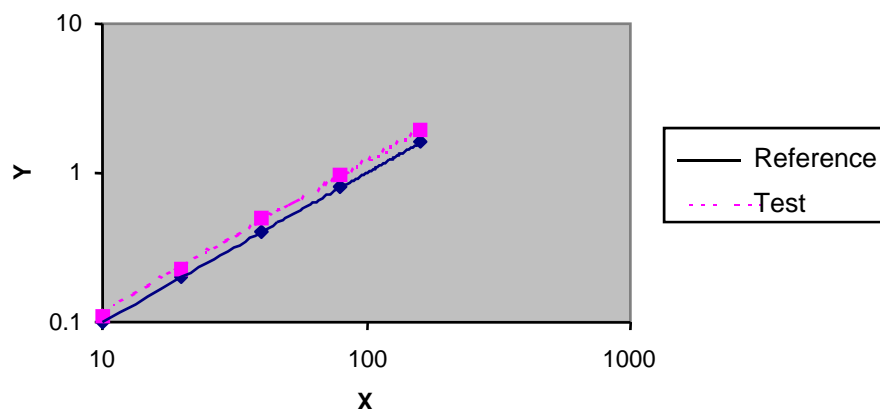
## USP Monograph for Growth Hormone

- ◆ When prepared as a lyophilized powder, it contains not less than 910 µg of somatropin per mg, calculated on the anhydrous basis
- ◆ When prepared as a bulk solution, it contains not less than 910 µg of somatropin per mg of total protein
- ◆ One mg of anhydrous Somatropin is equivalent to 3.0 USP Somatropin Units
- ◆ Maintenance of unitage within and across products is key to practitioner understanding of potency and dosimetry
- ◆ Basis for USP public monograph and national primary reference material



# USP: Promotes Open Science Discussion and Debate

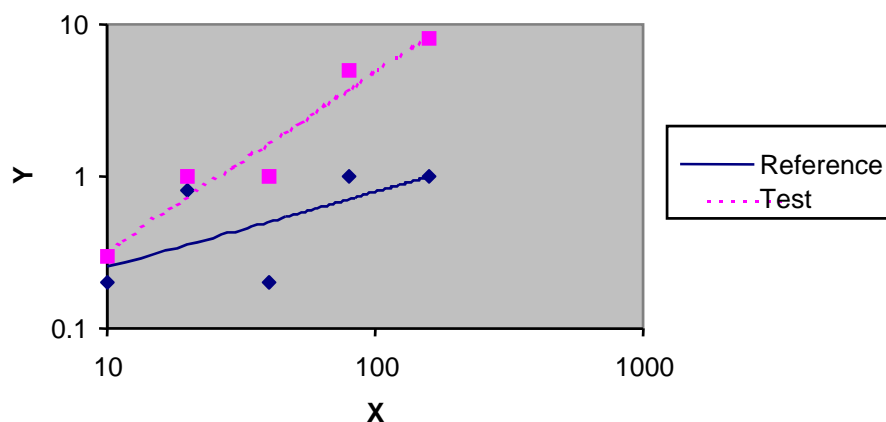
Laboratory A: Fails parallelism test



The run in Laboratory A fails the parallelism test because the low variability makes the test more sensitive

$$P < 0.05$$

Laboratory B: Passes parallelism test



The run in Laboratory B passes the parallelism test because the high variability makes the test less sensitive

$$P > 0.05$$



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*Thank You*