U.S. Pharmacopeial Convention

Global Expertise
Trusted Standards
Improved Health

Quality Approaches for Biologics

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Director, Biologics and Biotechnology

Topics

- Overview
- Comparability: FDA, ICH, EMA, WHO
- US FDA and Biosimilars
- Biological Products: Quality Attributes
- Role of the Pharamcopeias
- Closing Remarks

Biological Medicines: Opportunities and Challenges (1)

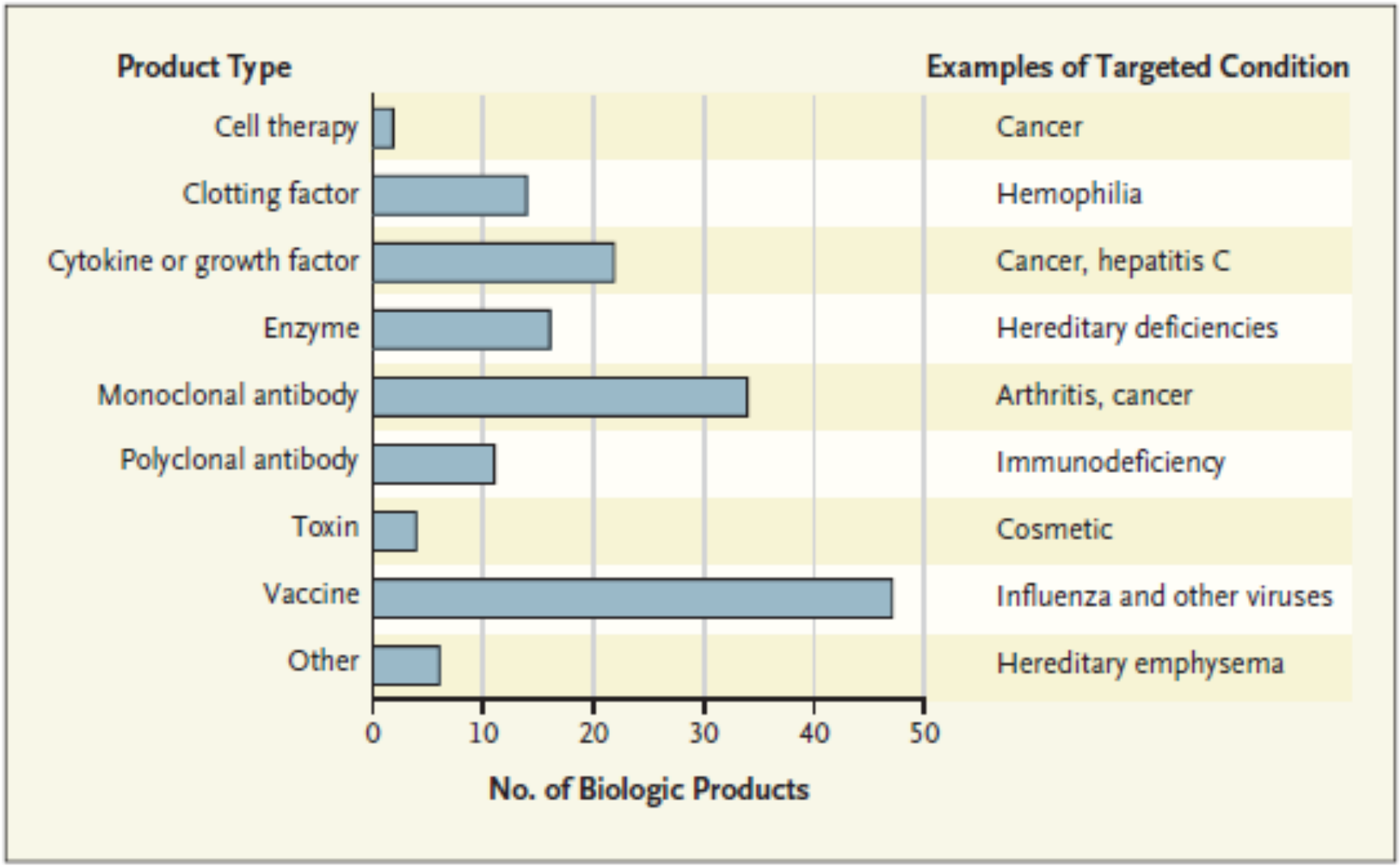
- Biological Medicines: Scope of Products
  - Blood and Blood Products
  - Cell, Gene, Tissue Therapies
  - Vaccines
  - Therapeutic Proteins, Recombinant and Naturally-derived
- Multi-components (e.g. raw materials) manufacturing:
  - Potential supply chain issues (e.g. animal derived materials)
  - Testing of quality of components before manufacturing begins
- Control of the quality, safety and efficacy of biologicals is difficult, despite technological advances
  - Orthogonal methods needed to address a single quality aspect
  - Higher order structures, often addressed by a biological assay

Biological Medicines: Opportunities and Challenges (2)

- Complex manufacturing processes with impact on:
  - Quality attributes of finished products
  - Challenging regulatory approval pathways

- U.S. Regulatory approaches:
  - Biologics = Subset of “Drugs”
  - Until recent biosimilars law passed, products approved through either the Federal Food, Drug, and Cosmetic Act (FDCA) or the Public Health Service (PHS Act) pathways
    - Depending on legacy approvals, sponsor preference, FDA Policy, and inter-center agreements

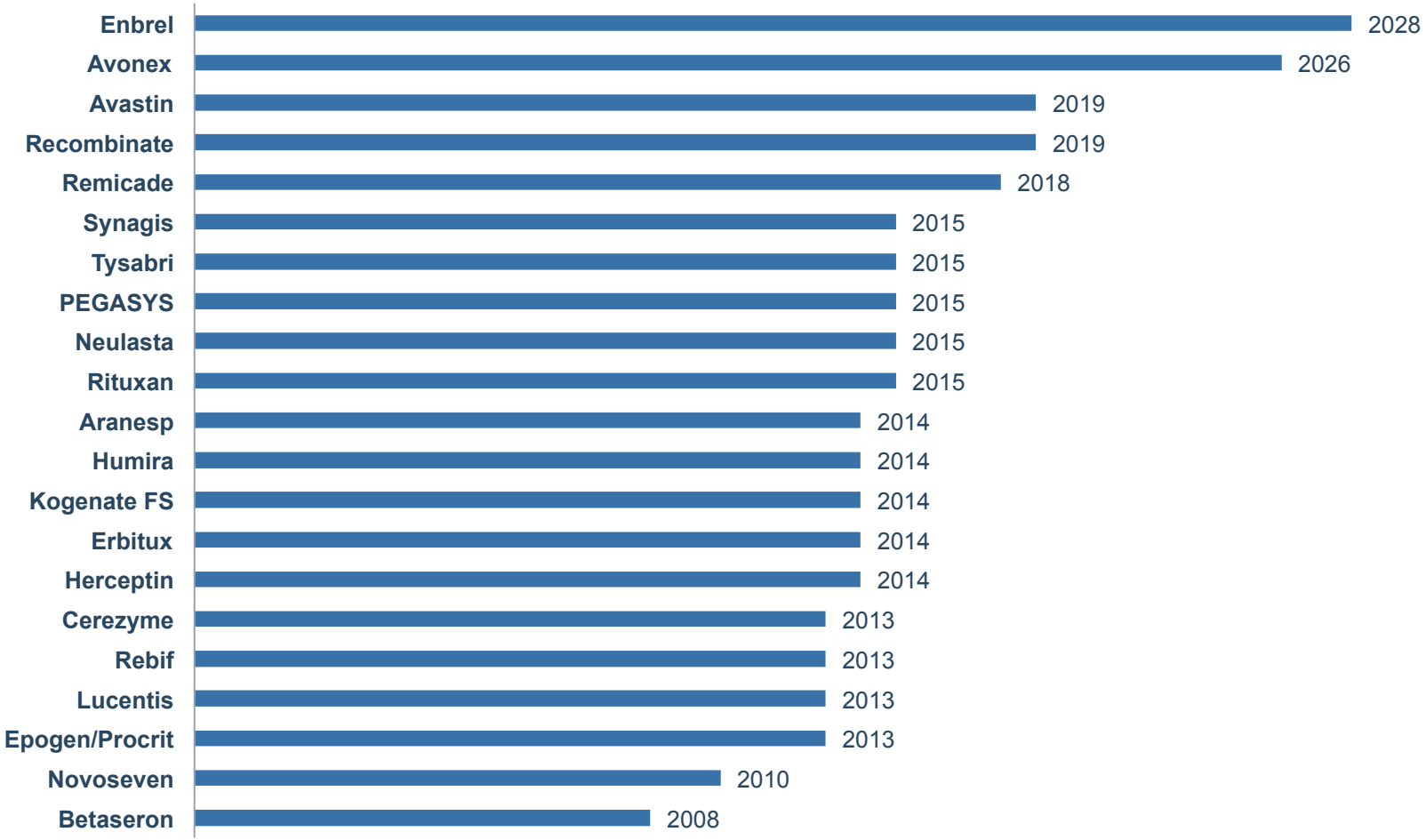
Current Biologics in the US Market



From Kozlowski et al., NEJM 265;5, 2011

Biologics with No Official USP Monograph

Patent Expiry Horizon



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FDA/CBER and ICH

- **CBER: Center for Biologics Evaluation and Research**
  1990s Comparability Guidance

- **Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process**
  The tripartite harmonised ICH guideline was finalised (Step 4) in November 2004. The objective of this document is to provide principles for assessing the comparability of biotechnological/ biological products before and after changes are made in the manufacturing process for the drug substance or drug product. Therefore, this guideline is intended to assist in the collection of relevant technical information which serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety and efficacy of the drug product. The document does not prescribe any particular analytical, nonclinical or clinical strategy. The main emphasis of the document is on quality aspects.
- **Final: September 2004**
- **Comparability: One-Way Interchangeability**

- EMA
  - Comparability Exercise
  - Analytical, Non-Clinical, Clinical
  - No Interchangeability

- WHO Guideline
  - Follows EMA
  - Comparability Exercise
  - No Interchangeability

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FDA Timeline

- Pre- BPCIA
- BPCIA: 2009
- Public Hearing: November 2010
- NEJM Article: August 2011
- Guidance Documents: February 2012
- Public Hearing: May 2012
  - Demonstrating interchangeability
  - Obtaining reference product exclusivity
  - Naming issues
  - Clinical pharmacology evaluation of biosimilars
  - Additional topics

BPCIA: Biologic Price Competition and Innovation Act

Regulation of Biological Products

- **CDER (NDAs and BLAs)**
  - Insulin and analogs
  - Hormones and analogs
  - Therapeutic protein, natural and recombinant
  - Monoclonal antibodies
  - Oligonucleotides
  - Synthetic peptide
- **CBER (BLAs)**
  - Blood and Blood components
  - Plasma products
  - Medical devices
  - Vaccines
  - Allergenic extracts
  - Cell and gene therapy
  - Xenotransplantation
  - Tissue

CBER: Center for Biologics Evaluation and Research
CDER: Center for Drug Evaluation and Research
NDA: New Drug Application
BLA: Biological License Application

Biologics Regulated by CDER

- **IND/NDA (FD&C Act)**
  - Insulin
  - Growth Hormone
  - FSH, LH, hCG, TSH
  - Calcitonin
  - PTH
  - Aprotinin
  - Hyaluronidase
  - Heparins
- **IND/BLA (PHS Act)**
  - Interferons
  - T-PA
  - Erythropoietin
  - Monoclonal Antibodies
  - Enzymes

IND: Investigational New Drug
NDA: New Drug Application
BLA: Biological License Application

Comparing and Contrasting BLAs and NDAs

- FDCA NDAs:
  - "Substantial Evidence" of safety and effectiveness; requires 1+ clinical studies; statutory bases for refusing approval, 505(d)
  - ANDAs truly abbreviated; *FDA "may not require" more info than listed in 505(j)(2)(A)*
- PHS Act BLAs:
  - Standard of "Safety, Purity and Potency," although considered by FDA to be interchangeable with "safety and effectiveness"
    (Biosimilars 'Scientific Considerations' Guidance, p. 3 fn 8)
  - Even biosimilars require 1 or more clinical studies "sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use . . . ."
    351(k)(2)(A)(i)(I)(cc); and see FDA Form 356h (Application to Market, 21 CFR 314 & 601)

What FDCA Requirements Apply to PHS Act BLAs?

- **PHS Act Recognizes Overarching Role of FDCA:**
  - PHS §262 (g): PHS may not be "construed as in any way affecting, modifying, repealing, or superseding" the provisions of the FDCA.
  - PHS §262 (j), added by 1997 FDA Modernization Act: The FDCA (including even 505 post-marketing studies, and REMS), applies to biologics approved with a PHS Act BLA, except 505 NDA not required.
- **All FDCA Requirements Except 505 License Apply**
  - IND Approval for Clinical Research *FDA Form 1571*
  - Post-approval adverse event reporting
  - Labeling not false or misleading
  - 503 Presc Drug Mktng Act *re Marketing, Samples, Distribution*
    505D Pharmaceutical Security
  - 501 & 502 Adulteration and Misbranding requirements
    - **GMPs (501(a)(2)(B))**
    - **USP Identity/Quality Standards (501(b); 502(e)(3)**
      USP Packaging & Labeling Standards (502(g))

By 2020, All "Biologic Products" Licensed With BLA

§351(k) "Biologic Product" defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, **protein** (except any chemically synthesized polypeptide), or analogous product, . . . , applicable to the prevention, treatment, or cure of a disease or condition of human beings." PHS §351(i)

After March 23, 2020, all legacy FDCA biologics will be deemed to be licensed under PHS §351 (see transition rules BPCI §7002(e))

By 2020, All "Biologic Products" Licensed With BLA (2)

Applicants seeking a BLA will continue to have two options:

- **PHS §351(a)**, based on a demonstration the biological product is "safe, pure and potent."

- **PHS §351(k)**, which requires one or more clinical studies "sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use," as part of information sufficient for FDA to determine that the biological product is "biosimilar" to a specified §351***(a)*** reference product, PHS §351(k)(2)((A)(i), ***and*** disclosure of confidential information, patent/exclusivity requirements. §351(l)

BPCIA (1)

- (A) IN GENERAL
  - (i) REQUIRED INFORMATION-An application submitted under this subsection shall include information demonstrating that-
    - **(I) the biological product is biosimilar to a reference product based on data derived from—**
      - (aa) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinical inactive components;
      - (bb) animal studies (including assessment of toxicity); and
      - (cc) A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.

BPCIA (2)

- **(II) the biological product and reference** product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product;
- **(III) the condition or conditions of use prescribed**, recommended, or suggested in the labeling proposed for the biologic product have been previously approved for the reference product;
- **(IV) the route of administration**, the dosage form, and the strength of the biological product are the same as those of the reference product; and
- **(V) the facility in which the biologic** product is manufactured, processed, packed, or held meets standards designed to assure that the biologic product continues to be safe, pure, and potent.

– (ii) DETERMINATION BY SECRETARY- The Secretary may determine, in the Secretary's discretion, that an element described in clause (i)(I) is unnecessary in an application submitted under this subsection.

– (iii) ADDITIONAL INFORMATION- An application submitted under this subsection—

- (I) shall include publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent; and
- (II) may include any additional information in support of the application, including publicly available information with respect to the reference product or another biological product.

- (B) INTERCHANGEABILITY- An application (or a supplement to an application) submitted under this subsection may include information demonstrating that the biological product meets the standards described in paragraph (4).

BPCIA (3)

- Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application (or a supplement to such application) is sufficient to show that—
  - (A) the biologic product—
    - (i) is biosimilar to the reference product; and
    - (ii) can be expected to produce the same clinical result as the reference product in any given patient; and
  - (B) for a biological product that is administrated more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

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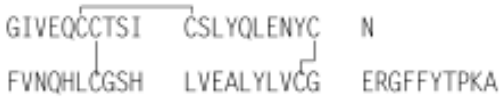
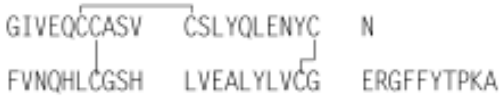
Definition – Insulin Example



$C_{256}H_{381}N_{65}O_{76}S_6$ 5777.55
Insulin (pig) [*12584-58-6*].



$C_{254}H_{377}N_{65}O_{75}S_6$ 5733.50
Insulin (ox) [*11070-73-8*].

» Insulin is a protein that affects the metabolism of glucose. It is obtained from the pancreas of healthy bovine or porcine animals, or both, used for food by humans. Its potency, calculated on the dried basis, is not less than 26.5 USP Insulin Units in each mg; Insulin labeled as purified contains not less than 27.0 USP Insulin Units in each mg, calculated on the dried basis. The proinsulin content, determined by a validated method, is not more than 10 ppm.

NOTE—One USP Insulin Unit is equivalent to 0.0342 mg of pure Insulin derived from beef or 0.0345 mg of pure Insulin derived from pork.

Questions of Identity

From *USP General Notices*

A compendial test titled Identity or Identification is provided to establish the identity of an article as it is purported to be, i.e., whether it is the article named in USP-NF. The Identity or Identification test for a particular article may consist of one or more procedures. When a compendial test for Identity or Identification is undertaken, all requirements of all specified procedures in the test must be met to satisfy the requirements of the test. Failure of an article to meet all the requirements of a prescribed Identity or Identification test (i.e. failure to meet the requirements of all of the specified procedures that are components of that test) indicates that the article is mislabeled and/or adulterated.

Elements of Identification for Biological Products

- Orthogonality
  - More than one test should be used to demonstrate identity, each test should measure a different attribute of the molecule
- Specificity – see USP <1225> *Validation of Compendial Procedures* and ICHQ2R1
  - Identification Tests require the demonstration of specificity as the primary goal in validation
- Activity/function
  - May be called out separately as *Bioidentity*
  - May also be part of the Definition

Identification – Example 1: Insulin Human

Identification—

- A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.
- B: Determine the peptide fragments, using the following peptide mapping procedure.

Identification and other Tests are often linked

Production System Differences

- Calcitonin Salmon is a polypeptide that has the same sequence as that of the hormone that regulates calcium metabolism and is secreted by the ultimobranchial gland of salmon. It is produced from either synthetic processes or microbial processes using recombinant DNA (rDNA) technology. The host cell-derived protein content and the host cell- or vector-derived DNA content of Calcitonin Salmon produced from an rDNA process are determined by validated methods. It contains not less than 90.0 percent and not more than 105.0 percent of calcitonin salmon, calculated on an acetic acid-free and dried basis.

Expression Systems and Identification

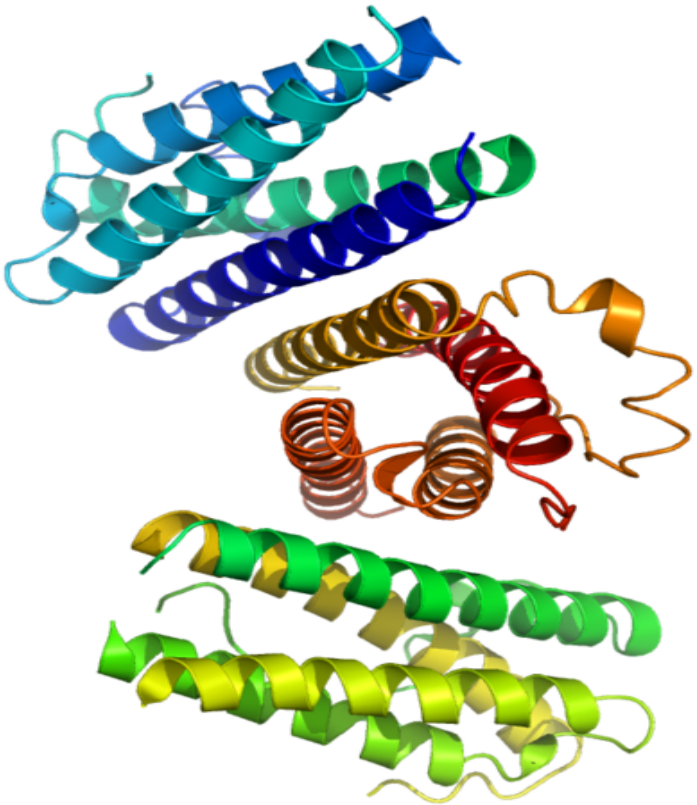
In *Calcitonin Salmon*:

Identification – The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, obtained as directed in the Assay.

Amino acid profile (see Biotechnology-Derived Articles – Amino Acid Analysis 1052)

[NOTE—This test needs to be performed only on material of synthetic origin.]

Filgrastim: G-CSF?



- Granulocyte colony stimulating factor (G-CSF)
- 18-20 kDa
- Hematopoetic cytokine that acts on cells of the neutrophil lineage causing proliferation, differentiation and activation of committed precursor and mature neutrophils.
- Used in treatment of neutropenia following chemotherapy
- 174 Amino acids, 2 intra-molecular disulfide bonds, one free Cysteine at residue 17 and one O-linked carbohydrate chain at Thr 133 (<4% of the molecular mass).
- Recombinant human G-CSF synthesized in an *E.coli* expression system is called Filgrastim

Protein Data Bank data (PDB: 1RHG)
Hill, C.P., Osslund, T.D., Eisenberg, D. The structure of granulocyte-colony-stimulating factor and its relationship to other growth factors. Proc.Natl.Acad.Sci.USA v90 pp.5167-5171, 1993

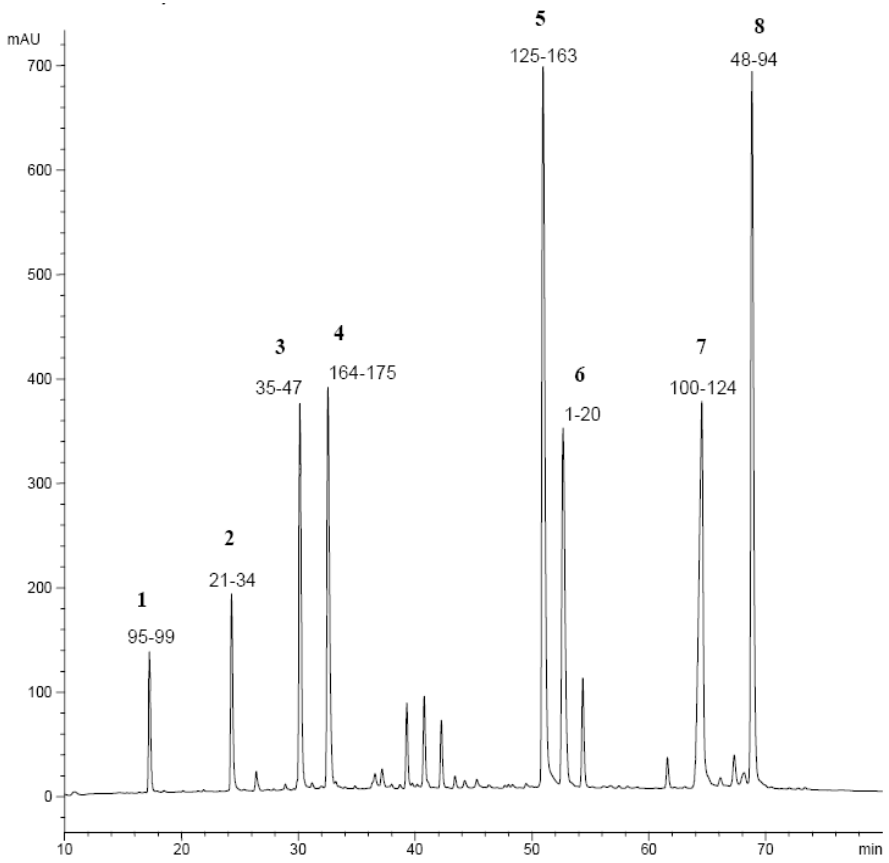
Filgrastim Drug Substance Monograph

- 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
- Assay (Potency)
- Impurities
- Additional Requirements
  - Packaging and Storage; Labeling
- Reference Standards

Filgrastim Monograph: *Identification*

- A. It meets the requirements described under Assay.
  - Acceptance criteria: It has a biological potency of NLT 80% and NMT 125%.
- B. It meets the requirements described under *Chromatographic purity*.
  - Acceptance criteria: NMT 1.0% of reduced Filgrastim is found and NMT 2.0% of total impurity is found.
- C. Peptide mapping with UV detection
  - Acceptance criteria: next slide

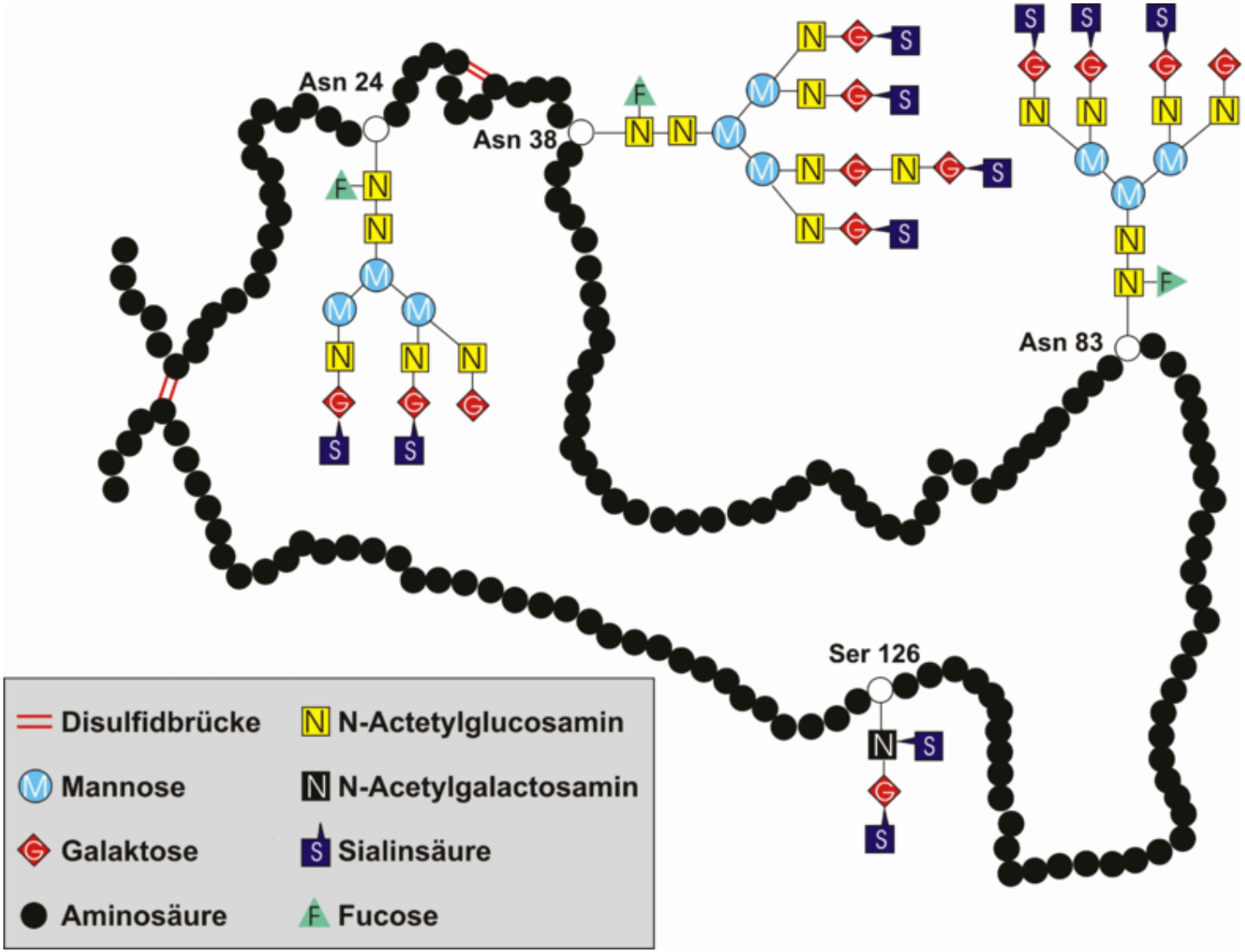
Identification C: Peptide Mapping with UV Detection



NOTE: 8 major peaks will be defined in the USP Filgrastim RS Data Sheet.

Acceptance criteria: The difference in retention of each of the eight major peaks between the *Test solution* chromatogram and the average of the *Standard solution* chromatograms must be ≤ 0.5 min. The relative difference in peak height between the normalized sample peak height and the average standard peak height of each of the eight major peaks must be ≤ 15%.

Erythropoietin (EPO), Structure and Glycosylation



Erythropoietin, Licensed in Europe - Examples

EPO	Brand name	Marketer/ Manufacturer	Reference product/ Comparator
Alpha	EPREX/ERYPO	JANSSEN/J&J	----------
Alpha	BINOCRIT **(Biosimilar)**	SANDOZ/Novartis	Epoetin alpha EPREX
Alpha	EPOETIN ALFA HEXAL**(Biosimilar)**	HEXAL/Novartis	Epoetin alpha EPREX/ERYPO
Zeta	SILAPO **(Biosimilar)**	Stada	Epoetin alpha EPREX
Beta	NeoRecormon.	Hoffmann-La Roche AG	----------
Theta	BIOPOIN, RATIOEPO **(Stand alone, non biosimilar)**	RatioPharm	Epoetin beta (comparator)

Erythropoietin- Different Molecules?

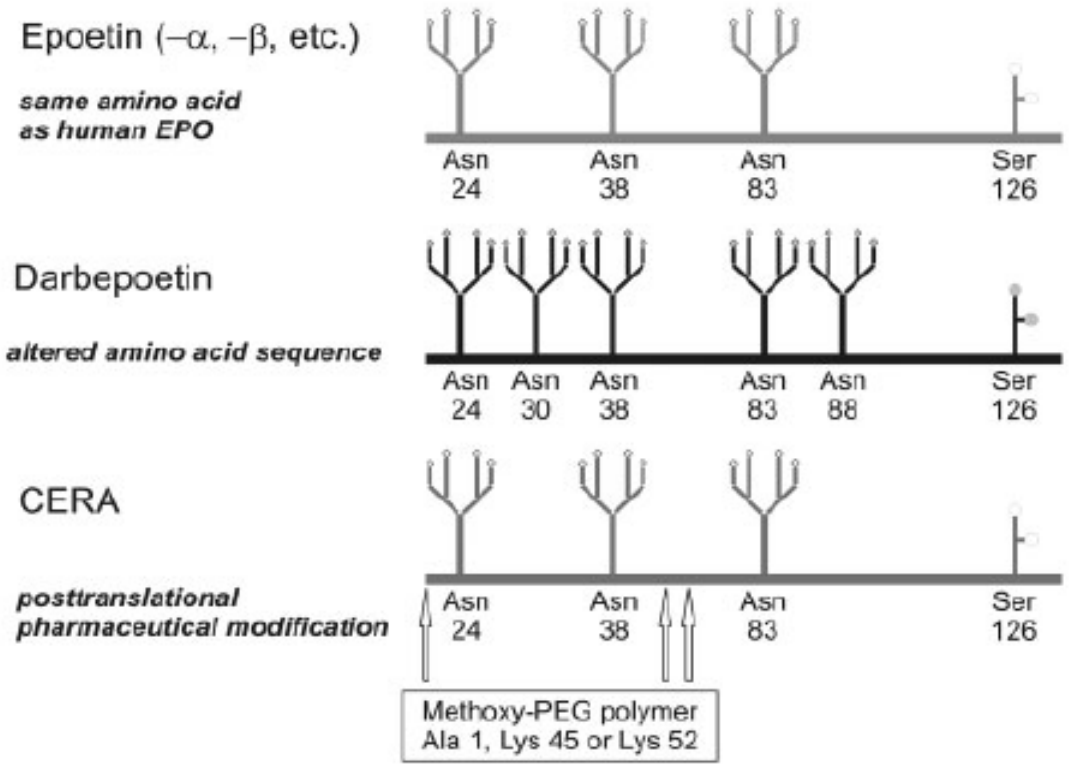
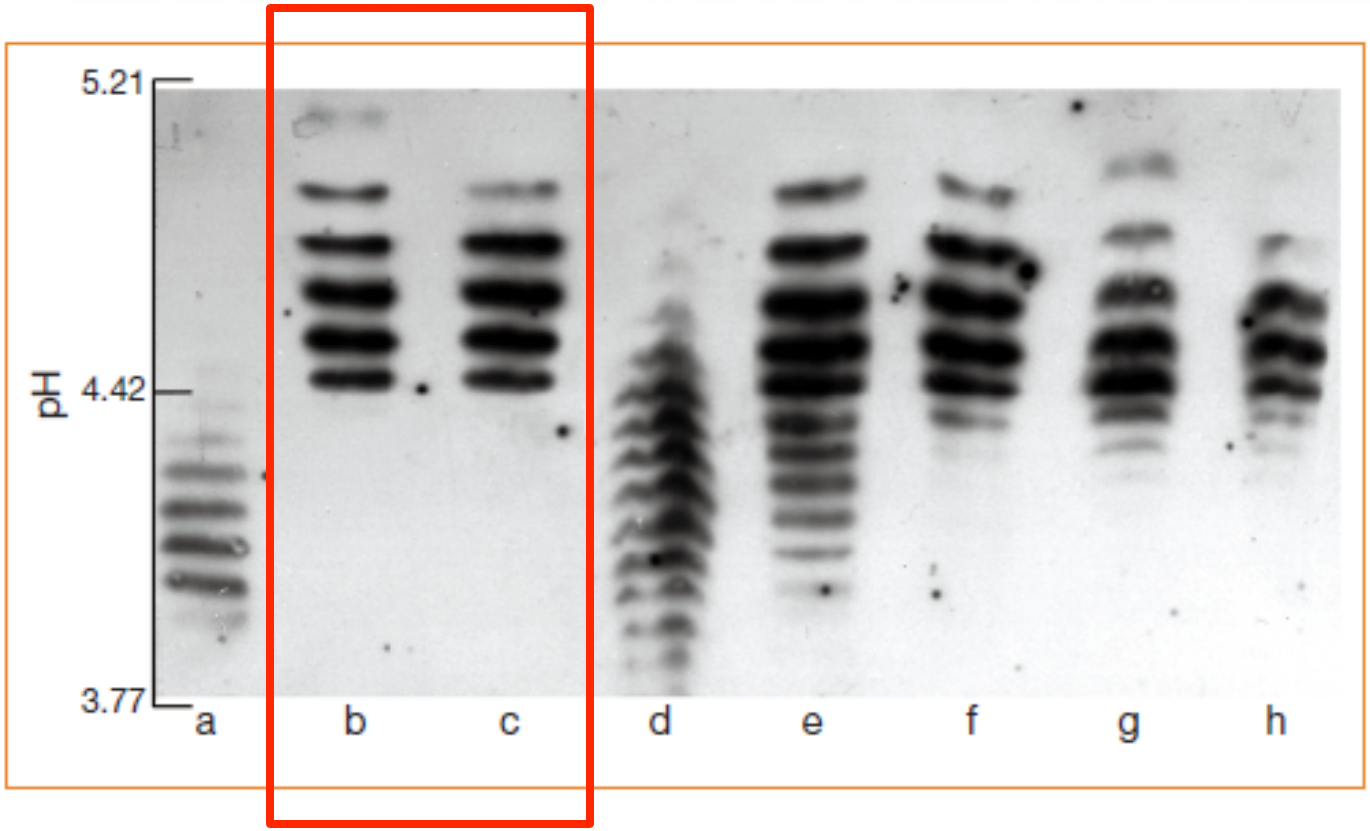


Fig. 2. Scheme of epoetin (EPO), darbepoetin and CERA (pegylated epoetin-β) and their glycosylation, respectively pegylation sites. While the amino acid sequence of all epoetins (α, β, ω, δ, etc.) is the same, they differ in the structure of their glycans and, thus, isoforms. Darbepoetin-α differs in five amino acids from epoetin and has two additional N-glycans.

Wolfgang Jelkmann **Recombinant EPO production—points the nephrologist should know**

Nephrol Dial Transplant (2007) 22: 2749–2753

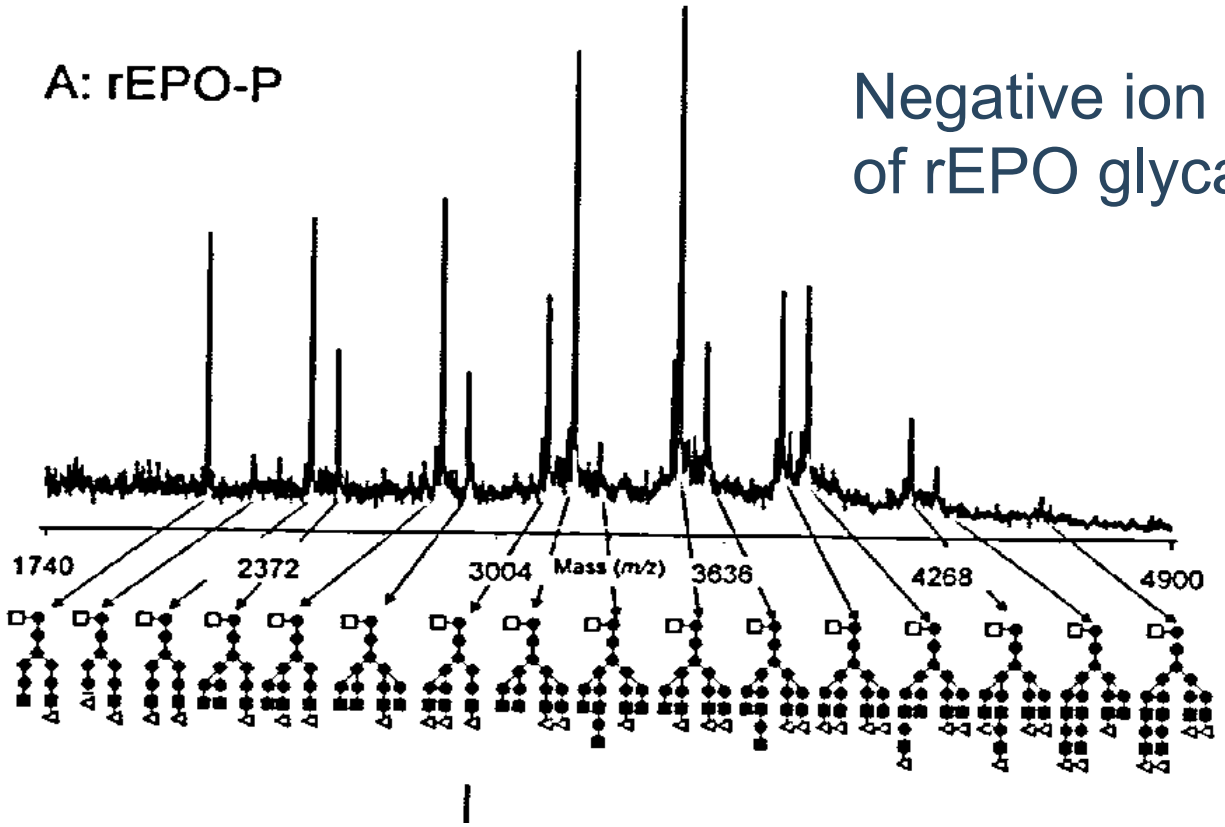
Isoelectric pattern of epoetin α and β



(a) Purified urine EPO, **(b) epoetin beta, (c) epoetin alpha**,
(b) (d,e,f,g,h) patients samples

Recombinant erythropoietin in urine, *Nature* 405, 635 (June 2000)
Françoise Lasne, Jacques de Ceaurriz

EPO's Glycosylation Microheterogeneity



Negative ion MALDI-MS of rEPO glycans

- Difference between epoetins is at the level of glycosylation Microheterogeneity

- The effect of glycosylation microheterogeneity on the molecule's bioactivity is complex and still scientifically controversial

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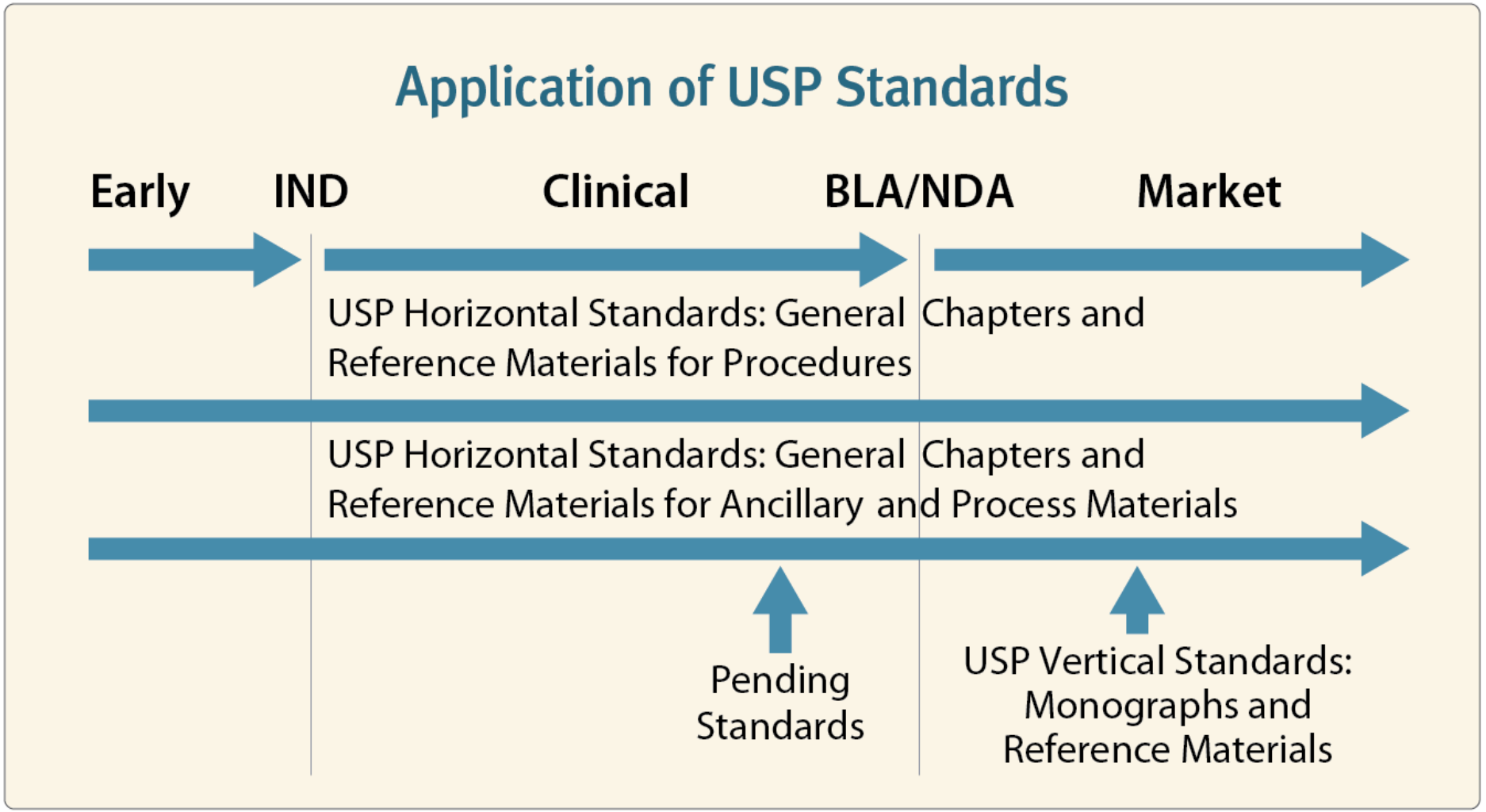
USP Compendia

1. The *United States Pharmacopeia*
2. *National Formulary* (*USP–NF*)
3. *Food Chemicals Codex (FCC)*
4. *USP Dietary Supplements Compendium (DSC)*
5. USP *Medicines Compendium (MC)*
6. USP on Compounding
7. *Herbal Medicines Compendium (HMC)*

- Other Resources
  - *Pharmacopeial Forum (PF)*
  - *FCC Forum (FCCF)*
  - *USP Dictionary*
  - *Chromatographic Columns*

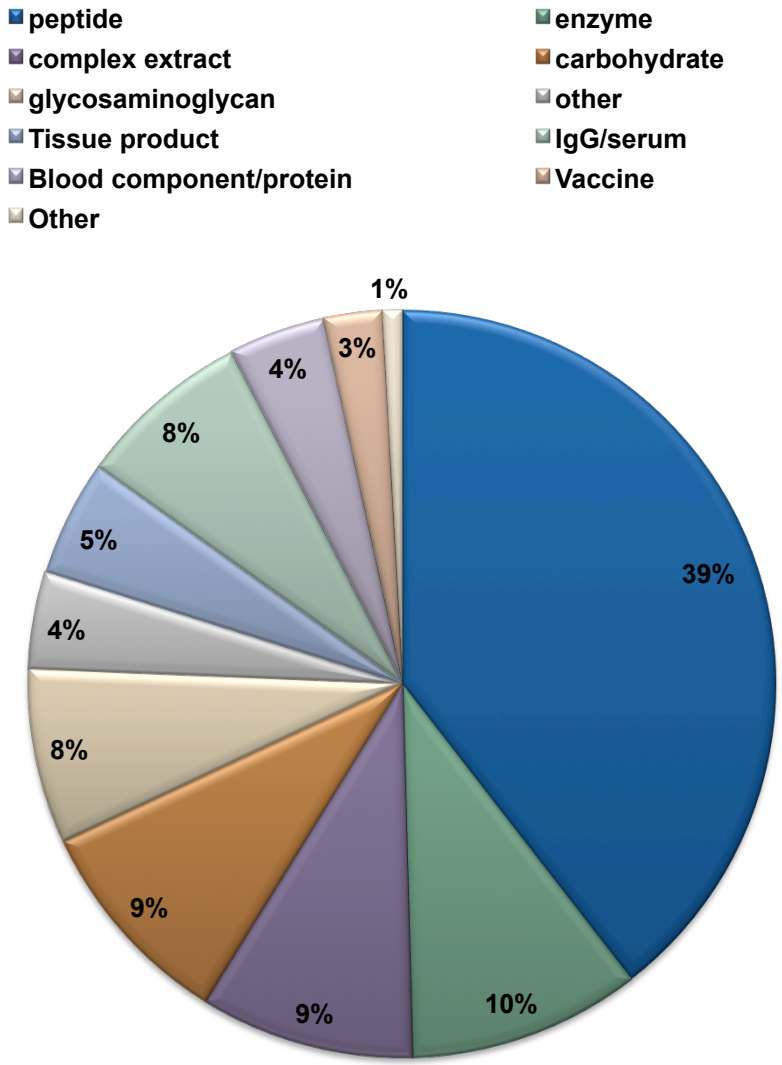
COMPOUNDING

USP Standards—Biologicals



Official USP Biologics Monographs by Product Class

B&B Overall Monograph Distribution by Product Class



Product Class	Number of monographs
peptide	47
enzyme	12
complex extract	11
carbohydrate	11
glycosaminoglycan	9
other	5
Tissue product	6
IgG/serum	9
Blood component/ protein	5
Vaccine	3

Biotech Products – Quality Testing and Monographs

- Identification
  - Retention Time from chromatographic assay
  - Peptide Mapping
  - N-Terminal Sequencing
- Purity
  - HPLC (Reverse Phase)
  - Limit on High Molecular Weight Species (Size Exclusion)
  - Glycoforms (Isoelectric focusing)
- Potency
  - Chromatographic when possible
  - Bioassay-Bioidentity
    - To address secondary and tertiary structures
    - Cellular preferred over animal
- Monographs also cover sterility, and other general requirements such as labeling, packaging and storage

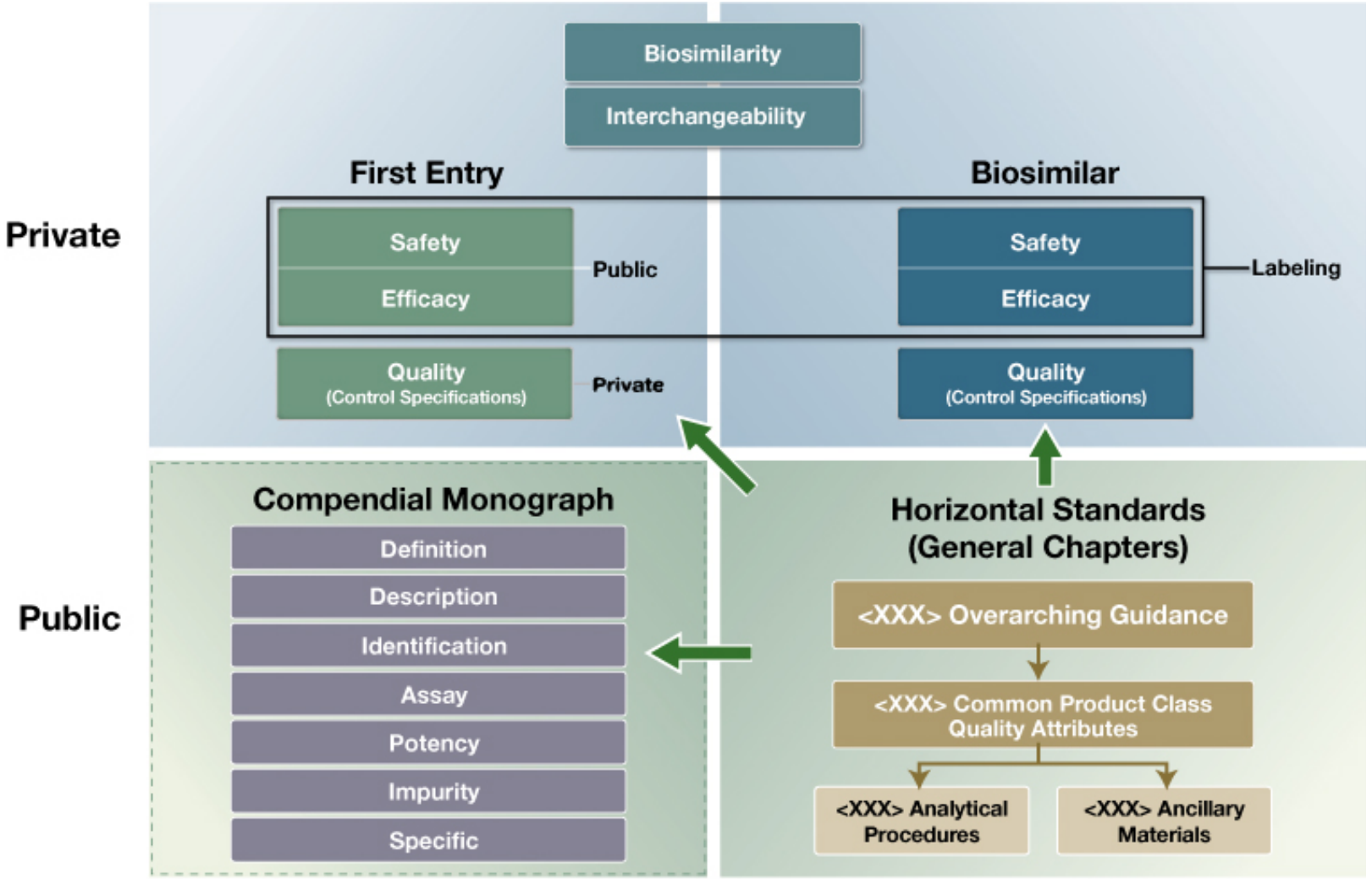
Peptide/Small Protein Drug Substance Monographs

	Somatropin	Insulin Human	Glucagon	Filgrastim
Identification - HPLC	X	X	X	X
Identification - Peptide Mapping	X	X	X	X
Assay - HPLC	X	X	X	
Impurities – related proteins: HPLC (Assay)	X	X	X	X
Impurities – Charge variants, IEF				X
Impurities – Limit of HMW proteins: SEC	X	X		X
Specific Tests: bioidentity, <85>, <61>/<62>, <731>	X	X	no bioidentity test for DS	no <731>

Horizontal Standards

From General to Specific—Biological Potency

Biologics Standards



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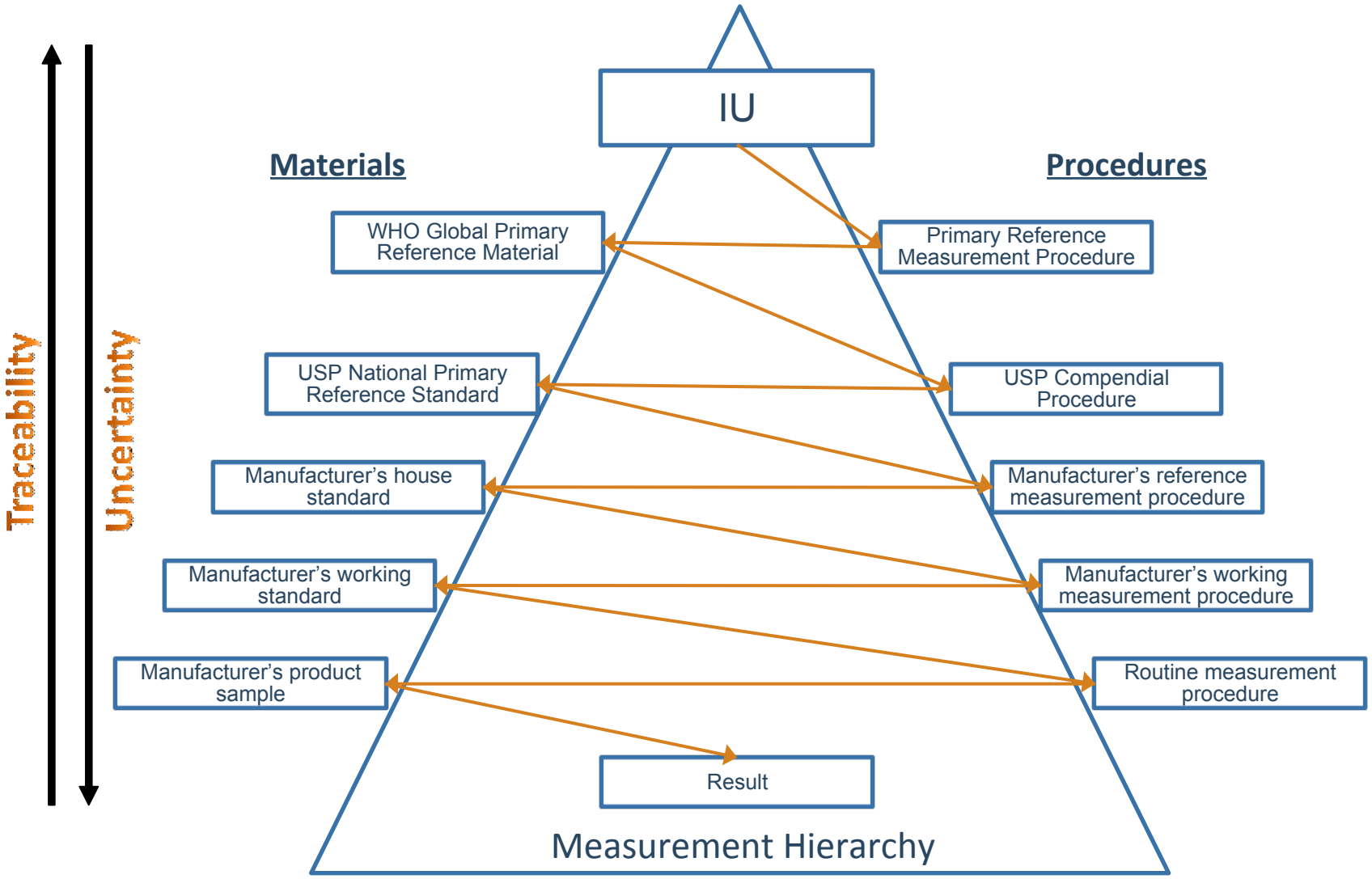
Metrology: Towards a Global Understanding

The Ideal State



Summary

- Public Standards Are Not Nice to Have, They Are Critical for Patient Protection and Consumer Confidence
- For Biologics, a Key Test in the Public Documentary Standard is the Biologic Potency Test(s)
- Physico-chemical Tests Are Also Critical
- A National Unit Should Trace to a WHO International Unit
- The Approach Is Time Honored, Starting with Insulin (or Before)
- Manufacturers and Regulatory Agencies Determine Subdivisions—Reference Products, Biosimilars, Interchangeable Biosimilars, and Generic (Copy) Biologics

Thank You