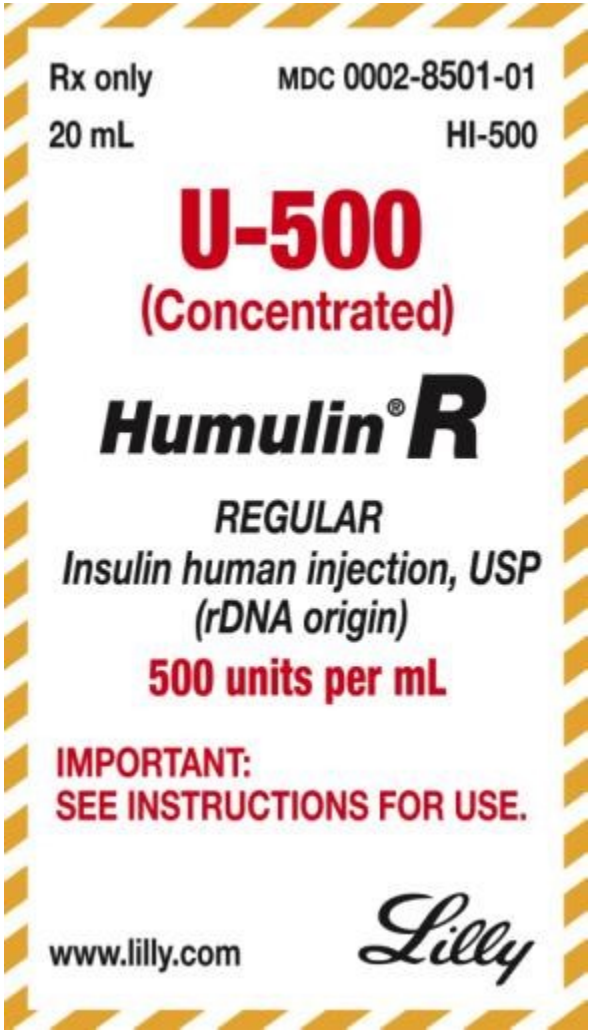
Global Expertise
Trusted Standards
Improved Health

U.S. Pharmacopeial Convention

Introduction to Drug Naming

Angela G. Long, M.S.
Senior Vice President, Global Alliances and Organizational Affairs

What's in a Name?



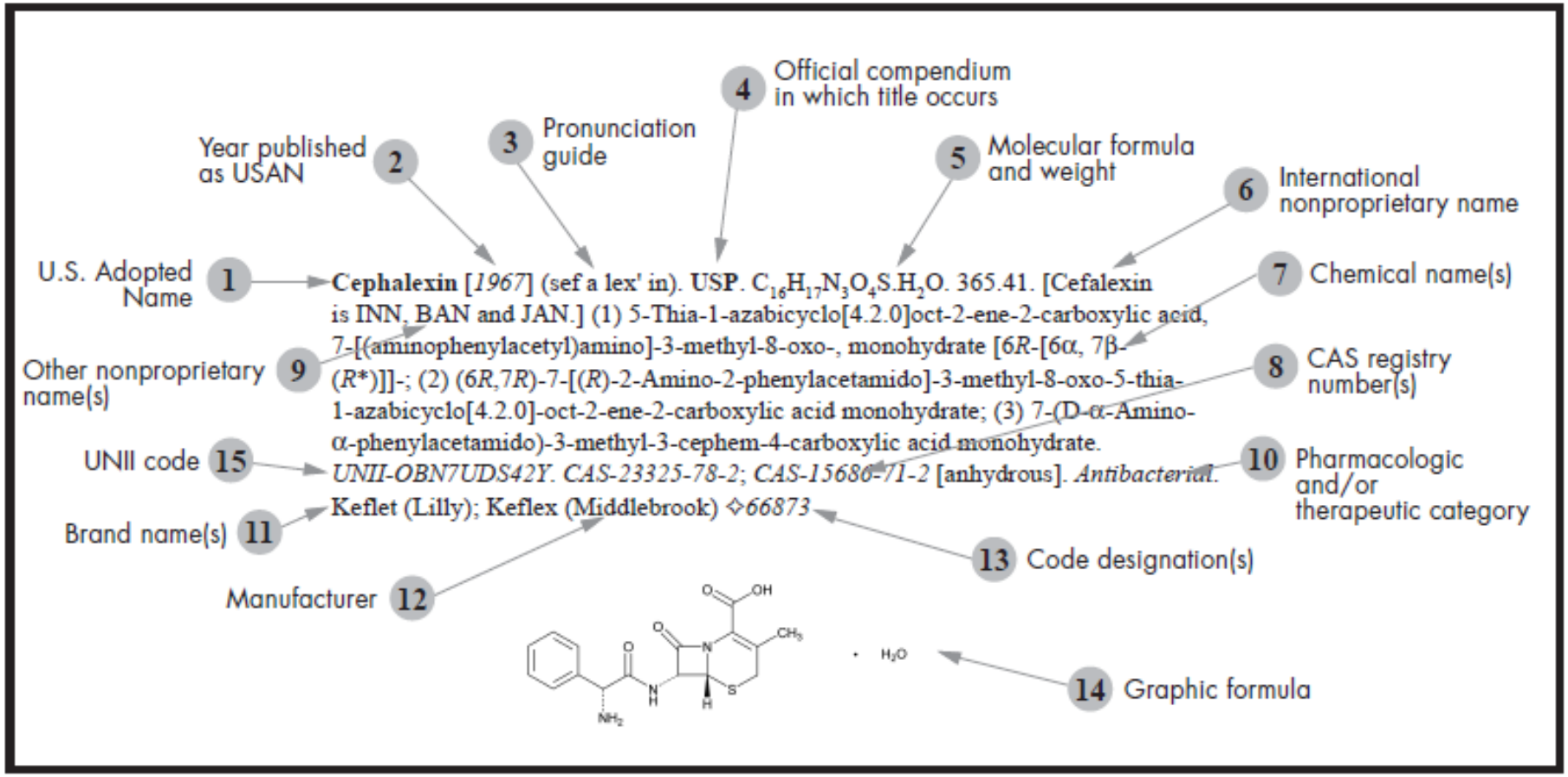
International Nonproprietary Names (INN)

- Sponsored by World Health Organization.
- Facilitates the identification of pharmaceutical substances or active pharmaceutical ingredients; nonbinding.
- INN is a unique name that is recognized to varying extents globally and is public property.
- The US does not follow INN; no role in federal law.

US Adopted Names Council

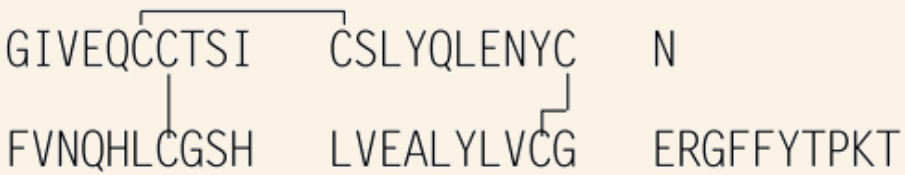
- The US Adopted Names Council plays a role in nonproprietary naming in the US.
- Sponsored by the American Medical Association, the American Pharmacists Association, and USP, with active participation by FDA.
- Works with INN but they are independent of each other.
- Drug substances only.
- Major role in naming drugs in development; 75% of USAN names don't make it to market.

USP-USAN Dictionary Entry



USAN Entry for Insulin Human

Insulin Human - (in′ su lin hue′ man).	
Date	[*1983*]
Official Compendia	**USP**.
Molecular Info	$C_{257}H_{383}N_{65}O_{77}S_6$. 5807.57.
Nonproprietary Name	INN; BAN.
Chemical Name	[Insulin Human (Biosynthesis) and Insulin Human (Synthesis) are JAN.] A protein that has the normal structure of the natural antidiabetic principle produced by the human pancreas. Insulin (human).
UNII Codes	*UNII-1Y17CTI5SR*.
CAS Numbers	*CAS-11061-68-0*.
Category	*Antidiabetic*.
Manufacturer Info	Humulin (Lilly); Novolin (Novo Nordisk); Velosulin (Novo Nordisk)



Biologics Naming: INN/USAN

- INN and USAN are working toward alignment; negotiations are aimed at achieving consensus.
- They both use similar approaches for naming biologics
  - Defining characteristics for biopolymers is the primary sequence
  - Biopolymers (proteins) with different glycosylation pattern are differentiated using a Greek suffix
  - Further elements of the name can include numbers (Interferon Alfa – 2a)
- At a recent INN meeting (April 15-18, 2013), a consensus emerged to develop a naming convention for biosimilars.
- At a public INN meeting (October 2013), INN suggested a classification system for biosimilars, separate from the INN.

USP Naming/Nomenclature in the Law

- If there are already applicable USP standards (determined by USP monograph Identity) when FDA approves a drug or biologic for marketing the “official title” in the USP monograph must be used as the official name for the drug substance and product (the Federal Food, Drug, and Cosmetic Act specifies that a drug with a name recognized in USP must comply with USP’s quality standards or be deemed adulterated or misbranded or both).
- When FDA approves a drug and there is no applicable USP standard—which is likely in the case of new chemical entities—FDA provides an “interim established name” that serves as the nonproprietary name until USP creates a monograph.

USP Naming/Nomenclature in the Law

- It's important to note that USP's broad role in naming applies to both drug substances and products, and to all drugs, including biologics licensed by FDA under the Public Health Service Act.
  - FDCA Adulteration and Misbranding provisions apply to PHS Act PHS Act 351(j)
  - USP quality standard and naming role is effectuated for a biologic article when a USP monograph is published and becomes official
  - Although FDA and USP work closely on nomenclature policy, USP naming is not directly implicated under either USP rules, or Federal law, *until a compendial standard applies to a particular article*

Role of USP Naming/Nomenclature In Law

- Drug deemed **misbranded** unless its label bears the "**official title**" recognized in *USP-NF*. FDCA 502(e)(3)
- FDCA & PHS Act drugs recognized in *USP* are deemed **adulterated or misbranded** if they fail to meet *USP* standards for **identity, strength, quality or purity** (FDCA 501(b); 21 CFR 299.5) **packaging & labeling** (FDCA 502(g))
- FDA-approved names in NDAs and BLAs are considered by FDA to be "**interim established names**," that exist only unless and until USP designates a name. See, e.g. *Novartis* v. *Leavitt*, 435 F.3d 344 (D.C.Cir. 2006)
  - FDA name may have to change: "The USP Nomenclature Committee acts under its own schedule, so that its designation of a name qualifying under §352(e)(3)(B) need not coincide with the FDA's approval of a drug."
    Novartis v. Leavitt, 435 F.3d 344, 352 (D.C. Cir. 2006).

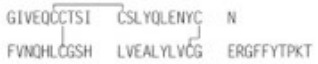
Summarizing USP's Role in Law

- A drug/biologic "shall" be deemed **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." FDCA 201(j), 501(b)
- If USP has an applicable monograph (Identity), the drug/biologic is deemed **misbranded** unless its label bears the **"official title"** (naming) recognized in *USP*. FDCA 502(e)(3)
  - While it rarely happens that a USP Expert Committee would approve a monograph containing a nonproprietary name in the title that differs from that in the FDA license (e.g. a BLA 'proper' name), it is possible.
  - Congress did give FDA authority to specify a USP official title/name; but it cannot be done in an NDA or BLA – the only way to override USP is by using notice and comment rulemaking. FDCA 508

USP's Role in Naming

- USP's role in naming applies to both **drug substances** and **drug products**

Insulin Human



$C_{257}H_{383}N_{65}O_{77}S_6$ 5807.57
Insulin (human) [11061-68-0].

» Insulin Human is a protein corresponding to the active principle elaborated in the human pancreas that affects the metabolism of carbohydrate (particularly glucose), fat, and protein. It is derived by enzymatic modification of insulin from pork pancreas in order to change its amino acid sequence appropriately, or produced by microbial synthesis via a recombinant DNA process. Its potency, calculated on the dried basis, is not less than 27.5 USP Insulin Human Units in each mg. The proinsulin content of Insulin Human derived from pork, determined by a validated method, is not more than 10 ppm. The host cell derived proteins content of Insulin Human derived from a recombinant DNA process, determined by an appropriate and validated method, is not more than 10 ppm. The host cell or vector derived DNA content and limit of Insulin Human derived from a recombinant DNA process that utilizes eukaryotic host cells are determined by a validated method.

NOTE—One USP Insulin Human Unit is equivalent to 0.0347 mg of pure Insulin Human.

Insulin Human Injection

» Insulin Human Injection is an isotonic sterile solution of Insulin Human in Water for Injection. It has a potency of not less than 95.0 percent and not more than 105.0 percent of the potency stated on the label, expressed in USP Insulin Human Units in each mL.

*Fragment I consists of amino acids A5 to A17 and B1 to B13. Fragment II consists of amino acids A18 to A21 and B14 to B21. Fragment III consists of amino acids B22 to B30. Fragment IV consists of amino acids A1 to A4. A refers to the A-chain of Insulin Human, and B refers to the B-chain of Insulin Human.

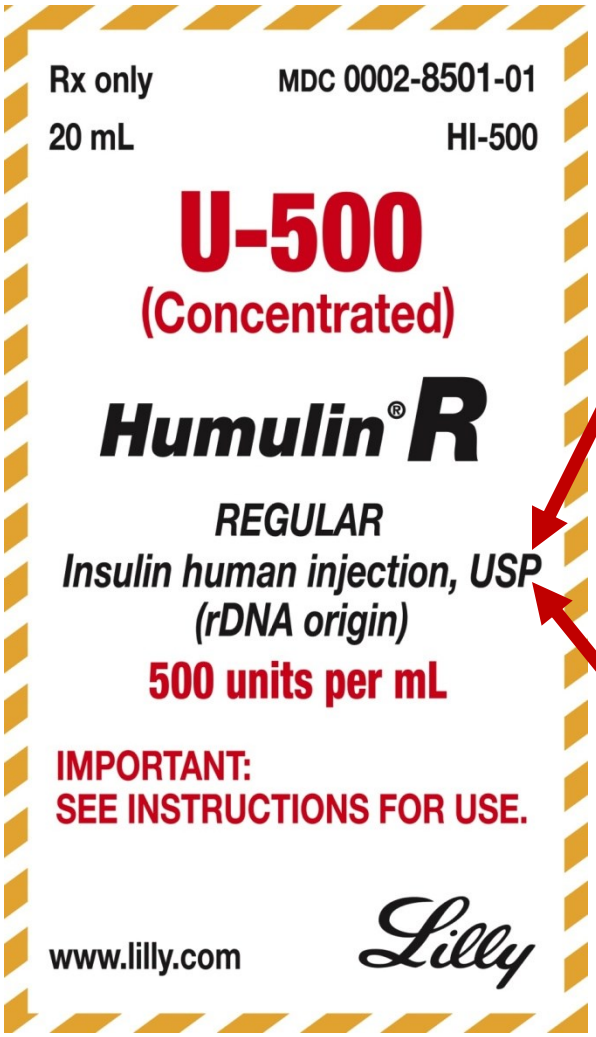
Packaging and storage—Preserve in a refrigerator. Protect from sunlight. Avoid freezing. Dispense it in the unopened, multiple-dose container in which it was placed by the manufacturer.

Labeling—The labeling states that it has been prepared either with Insulin Human derived by enzyme modification of pork pancreas Insulin or with Insulin Human obtained from microbial synthesis, whichever is applicable. Label it to state that it is to be stored in a refrigerator and that freezing is to be avoided. The label states the potency in USP Insulin Human Units per mL.

USP Reference standards ⟨11⟩—
USP Endotoxin RS
USP Insulin Human RS
USP Insulin (Pork) RS

Identification—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*.

The Nonproprietary Name Provides the Link to USP's Publicly Available Quality Standards



Insulin Human Injection

» Insulin Human Injection is an isotonic sterile solution of Insulin Human in Water for Injection. It has a potency of not less than 95.0 percent and not more than 105.0 percent of the potency stated on the label, expressed in USP Insulin Human Units in each mL.

*Fragment I consists of amino acids A5 to A17 and B1 to B13. Fragment II consists of amino acids A18 to A21 and B14 to B21. Fragment III consists of amino acids B22 to B30. Fragment IV consists of amino acids A1 to A4. A refers to the A-chain of Insulin Human, and B refers to the B-chain of Insulin Human.

Packaging and storage—Preserve in a refrigerator. Protect from sunlight. Avoid freezing. Dispense it in the unopened, multiple-dose container in which it was placed by the manufacturer.

Labeling—The labeling states that it has been prepared either with Insulin Human derived by enzyme modification of pork pancreas Insulin or with Insulin Human obtained from microbial synthesis, whichever is applicable. Label it to state that it is to be stored in a refrigerator and that freezing is to be avoided. The label states the potency in USP Insulin Human Units per mL.

USP Reference standards ⟨11⟩—
USP Endotoxin RS
USP Insulin Human RS
USP Insulin (Pork) RS

Identification—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*.

Bacterial endotoxins ⟨85⟩—It contains not more than 80 USP Endotoxin Units for each 100 USP Insulin Human Units.

USP's Expert Committees

- Nomenclature, Safety, and Labeling
  - Responsible for drug naming
  - Members with expertise in drug naming and backgrounds in pharmacy, nursing, medicine, biologics, and veterinary medicine from academia, industry, and various organizations
  - FDA liaisons from CDER and CVM
- Biologics Monographs Expert Committees
  - Establish USP's monograph quality standards
  - Members with expertise in biologics and backgrounds in industry, academia, and organizations;
  - FDA liaisons from CBER and CDER
- Work closely to ensure the name and monograph tests are linked

USP Perspective on Biosimilar Naming

- No USP role regarding brand names; unique brand names OK
- Once biosimilars are approved, if the drug meets the requirements of the USP identification test of an existing USP monograph, it should use the USP monograph title for its proper/official/established name (unless FDA designates an official name under FDCA 508, using notice and comment rulemaking)
- USP encourages FDA to pursue the idea of an ‘orange book’ for biologics

Global Expertise
Trusted Standards
Improved Health

U.S. Pharmacopeial Convention

Scientific Considerations for Naming Recommendations from USP's Biologics Expert Committees

Tina S. Morris, Ph.D.
Vice President, Biologics & Biotechnology

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"

USP Name and Compendial Identity

USP General Notices

5.40. Identity

A compendial test titled Identity or Identification is provided as an aid in verifying the identity of articles as they are purported to be, e.g., those taken from labeled containers, ***and to establish 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.*

What Does this Mean in Practice?

Somatropin

FPTIPLSRLF DNAMLRAHRL HQLAFDTYQE FEEAYIPKEQ KYSFLQNPQT
SLCFSESIPT PSNREETQQK SNLELLRISL LLIQSWLEPV QFLRSVFANS
LVYGASDSNV YDLLKDLEEG IQTLMGRLED GSPRTGQIFK QTYSKFDTNS
HNDDALLKNY GLLYCFRKDM DKVETFLRIV QCRSVEGSCG F

$C_{990}H_{1528}N_{262}O_{300}S_7$ 22,124.77 [12629-01-5].

Identity Tests:

1. Chromatographic Purity by HPLC
2. Peptide Mapping

Bioidentity: Bioassay

Several orthogonal procedures should probe different identifying attributes of the article, including the primary sequence.

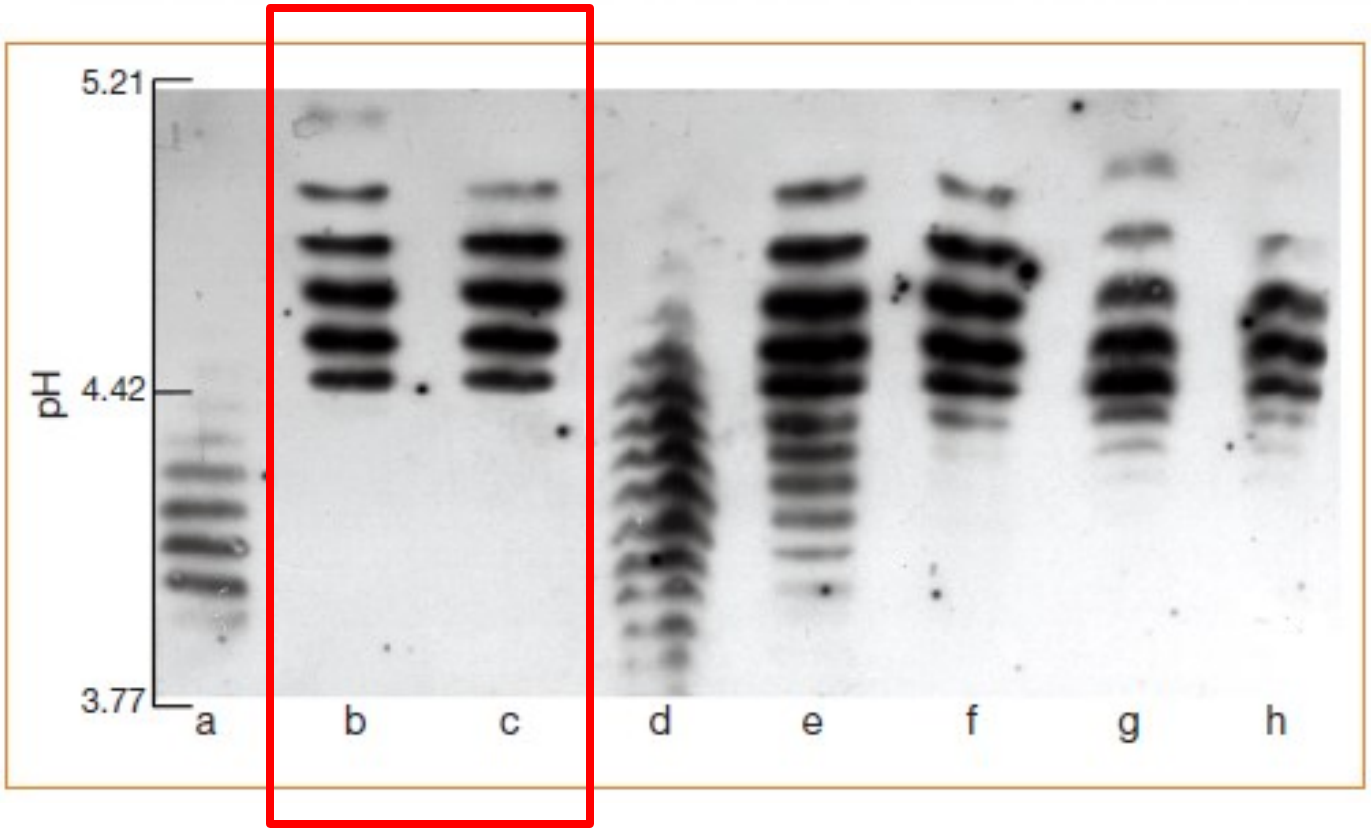
The Challenge of Glycosylation

Unlike the primary sequence of a protein, glycosylation is not a template-driven process, rendering it more variable and susceptible to changes that occur during molecule synthesis

It may or may not have an influence on the structural, functional, and clinical characteristics of the molecule – it may or may not be a critical quality attribute

The analysis of complex glycosylation patterns and the level of heterogeneity and microheterogeneity made visible is directly linked to the resolving power of the applied analytical technology

Isoelectric Patterns of Epoetin α and β



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

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

USP's Experience to Date

USP to date does not have an official monograph for a recombinant therapeutic that addresses glycosylation, but is currently considering a monograph proposal.

Typical deliberations by the USP Expert Committees include:

1. Consider the existing USAN name(s) and compendial standards in other pharmacopeias where they may exist
2. Consider proposed test(s), their specificity and resolving power in the context of the article identity and scope of the entire monograph
3. Reconcile proposal with previous and existing naming approaches in the compendium for biological medicines

Thank You