The Rigorous FDA Review Process for Biosimilars and Interchangeables

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Overview

- FDA's approach to the review and regulation of biosimilars
- Role of analytics in the development and licensure of biosimilars
- Scientific determination of when differences in products matter, and when they don't

Definition of Biosimilar*

Biosimilar Protein Product (≥ 40 AA):

Biological product *highly similar* to the reference product notwithstanding

- ***minor differences in clinically inactive components*; &**
- ***no clinically meaningful differences***

* *per* Biologics Price Competition and Innovation Act of 2009.

* *Definition abbreviated for purposes of this talk*

Development of a Biosimilar

① **Characterize US-licensed reference product using state of the art analytics**

② **Reverse engineer the Biosimilar**

③ **Perform extensive analytical comparisons between proposed biosimilar & reference product**

④ **Manipulate the process until achieve high degree of similarity (iterative)**

⑤ **Address residual uncertainties with functional, non-clinical and/or clinical studies**

Thanks to the power of today's powerful analytical tools…

Small differences between a biosimilar and a reference product are unavoidable and will be detected.

The challenge is how to rigorously justify any observed differences to ensure highly similar clinical performance.

Elements of Biosimilarity

from the 2012 FDA Scientific Considerations Guidance

351(k) application must contain information demonstrating that the product is biosimilar to a reference product based upon different types of studies:

- **Analytical**
- **Animal (including assessment of toxicity), &**
- **Clinical (PK, PD, immunogenicity, others) sufficient to demonstrate safety, purity, & potency** in one 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**.**

Agency has discretion to determine that an element described above is unnecessary in a 351(k) application.

FDA review decisions

FDA will not waive an element if the reviewers are uncertain that the product will have clinical activity that is highly similar to the US-licensed reference product.

FDA review process

- **Experienced reviewers with deep knowledge of protein products (track record)**
- **Numerous internal meetings & working groups on each product & review issue**
- **Multiple levels of supervision & oversight**
- **Teamwork:**
  - **Quality, Pharmacology-toxicology (non-clinical), Clinical Pharmacology (PK/PD), Clinical, Legal, Policy)**

The bottom line

- **The FDA will only approve a biosimilar that can *reliably be expected* to perform similarly to a US-licensed reference product**
  - **No motivation to do otherwise**
  - **Conservative, risk averse**
  - **All scientific and regulatory expertise brought to bear**
- **Any residual uncertainties need to be alleviated by Sponsor with data**
- ***Virtual interchangeability***

The Power of Modern Analytical Methods

Biosimilars are a reality today because of the enormous advances in analytical methods that allow deep & comprehensive evaluation of protein structure & function.

The foundation of the similarity assessment is the analytical studies.

Power of different types of studies to detect differences between products

- **Analytical Studies**
  - **Physicochemical/biochemical**
  - **Functional (Bioassays, binding)**
    - ***Animal Studies***
      - ***PK/PD/Biodistribution***
      - ***Toxicity***
- **Clinical Studies**
  - **PK/PD**
  - **Safety & Efficacy**

Higher

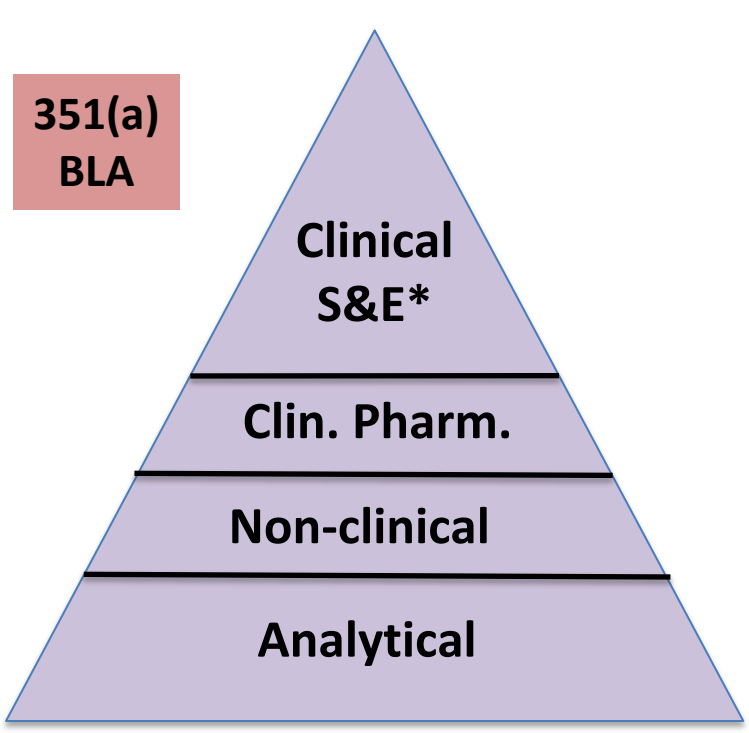
Lower

Sensitivity to Detect changes

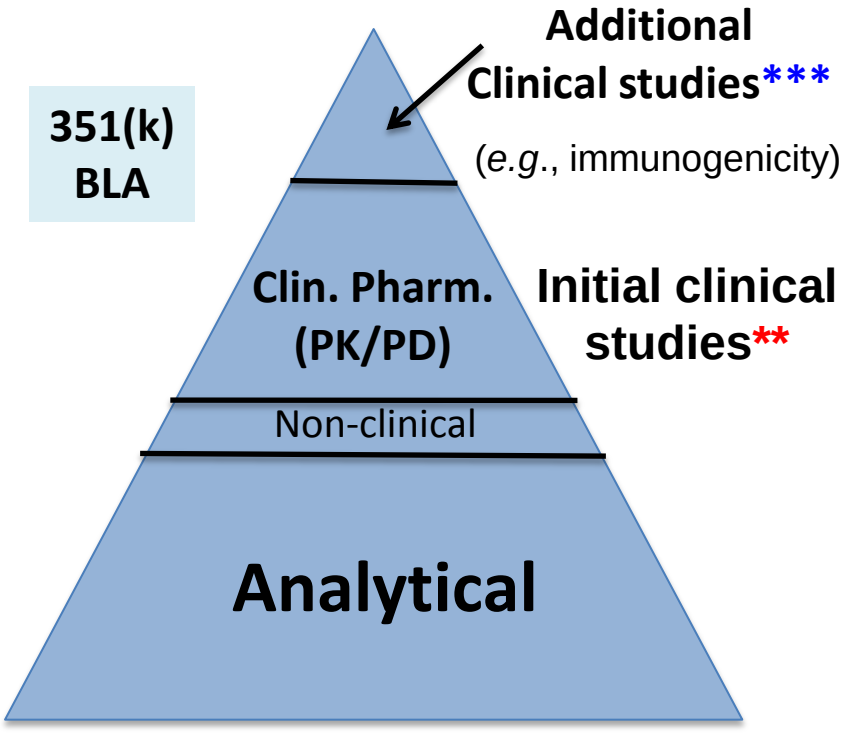
Role of Analytical *vs* Clinical Studies

Significant differences in molecular attributes cannot be overcome with clinical studies.

Biosimilars Development Paradigm



**Pivotal*



** Pivotal in biosimilars development

*** As needed

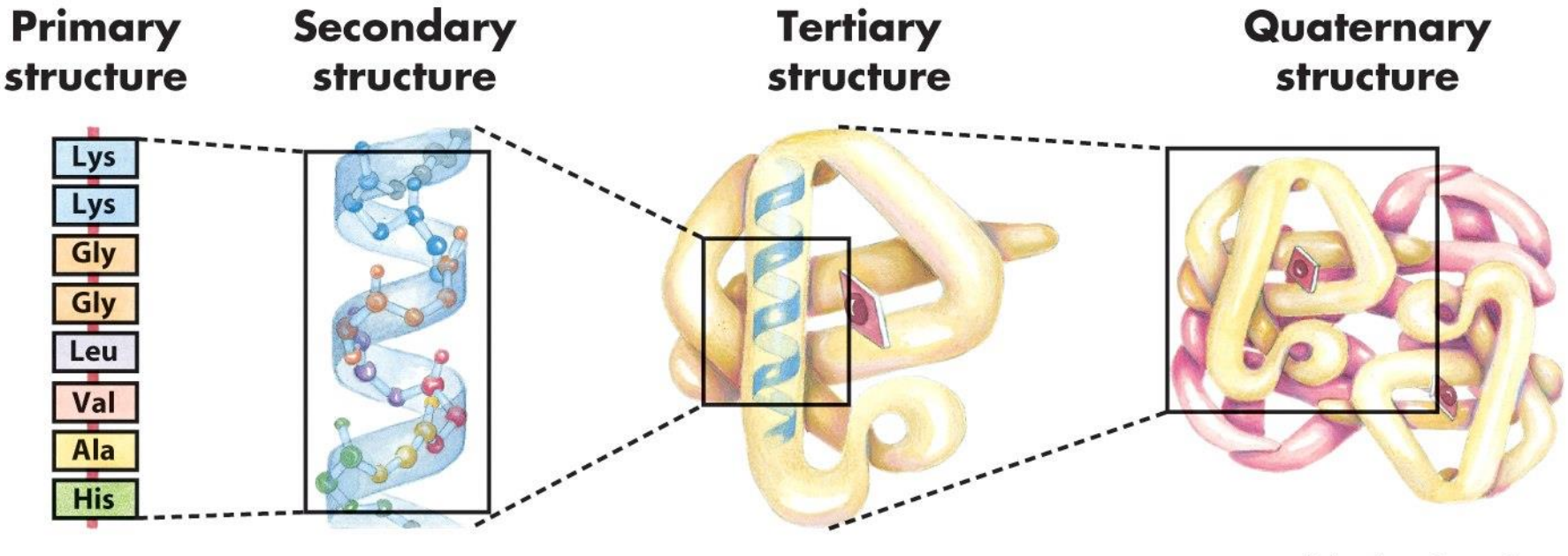
How do you get reduced non-clinical & clinical requirements for licensure of a biosimilar protein product?

Demonstrate and convince the FDA that your product is highly similar to a U.S.-licensed reference product.

And that ain't easy…

But can be done

Hierarchy of protein structure



Amino acid sequence charge, hydrophobicity (hp)

helix, β sheet, turns, loops

Folded polypeptide chain
Disulfide bonds, other forces
Functional Domains

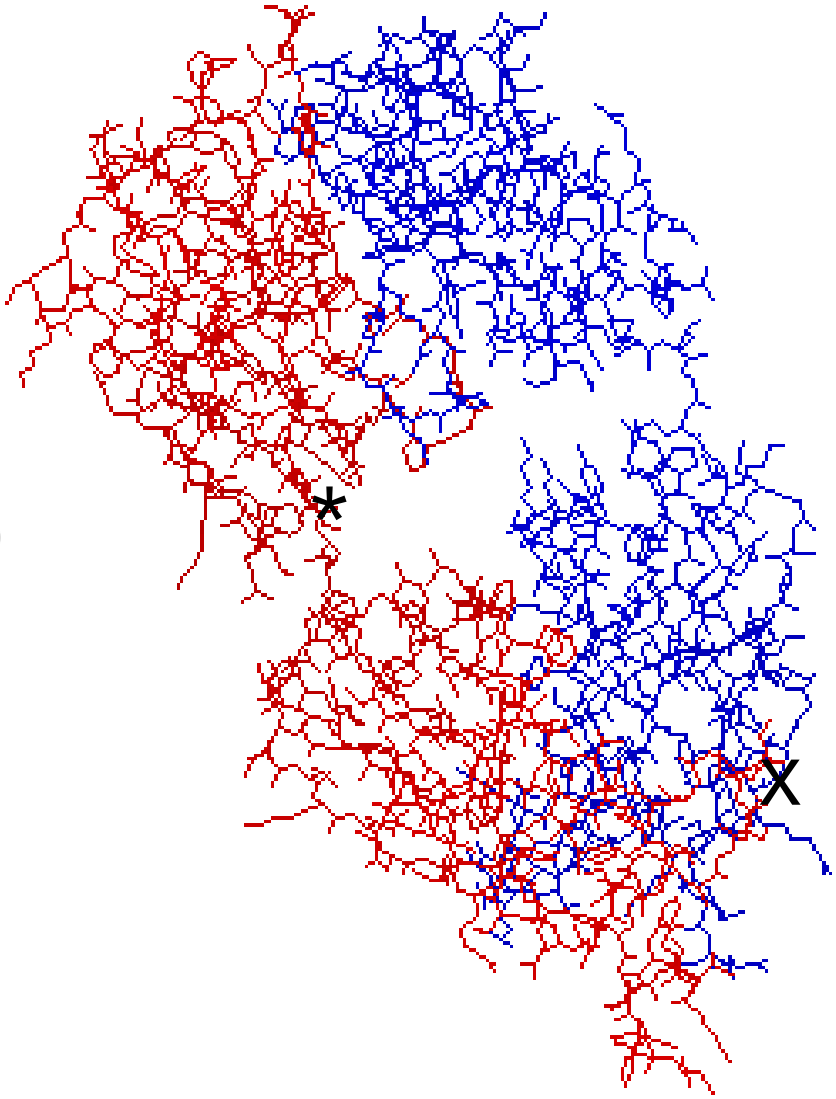
Subunits, protein-protein interactions, aggregates

All need to be evaluated as part of analytical similarity studies

Impact of molecular differences/variants on protein drugs

Proteins are heterogeneous mixtures of molecules with various:

- Amino acid side chain modifications
- Sequence modifications (sequence variants, truncations)
- S-S bonds
- Folding
- Subunit structures
- Size
- Charge
- Hydrophobicity
- Glycoforms
- Aggregates



Therapeutic protein ~5,000 - 300,000 Da

Thanks to modern analytical tools

Protein products CAN be deeply analyzed and characterized

Complexity of protein products is addressed with large array of powerful analytical tools

Analytical Tools to Evaluate Proteins

Amino acid sequence and modifications: Mass spectrometry (MS), peptide mapping, chromatographic separations

Folding: S-S bonding, calorimetry, HDX & ion mobility MS, NMR, X-ray, circular dichroism, Fourier transform & Raman spectroscopy, fluorescence, interaction chromatographies

Subunit interactions: chromatography, ion mobility MS

Heterogeneity of size, charge, hydrophobicity: Chromatography resins; gel & capillary electrophoresis, light scatter, ion mobility MS

Glycosylation Anion exchange, enzymatic digestion, peptide mapping, CE, MS

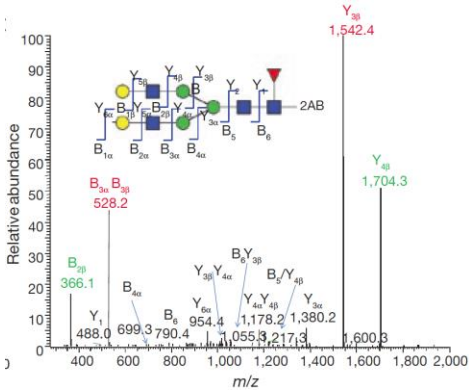
PEGylation & isomers: chromatography, peptide mapping

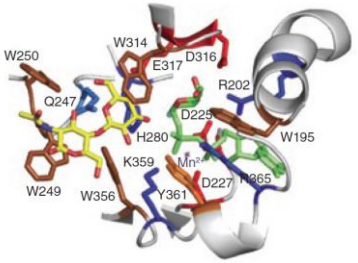
Bioactivity: cellular and animal bioassays; ligand & receptor binding (ELISA, surface plasmon resonance), signal transduction

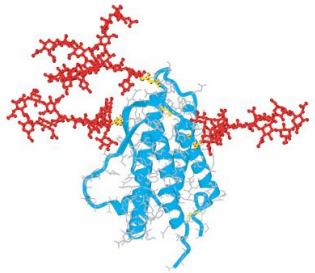
Aggregation: Analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, light scatter, microscopy

Proteolysis: electrophoresis, chromatography, MS

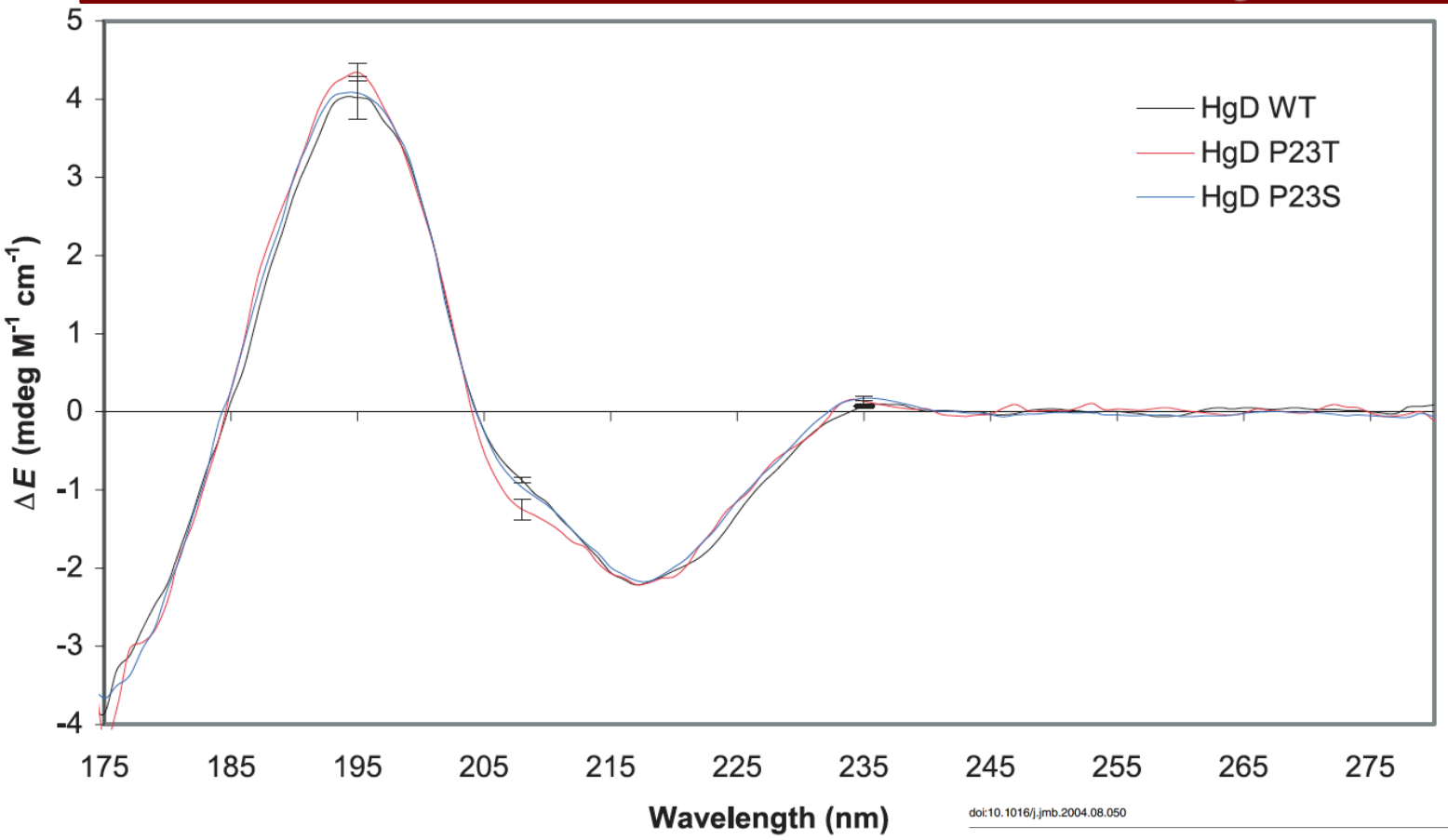
Impurities: proteomics (MS), immunoassays, PCR, metal & solvent analysis







Synchrotron Resonance CD spectra of cataract-associated mutation in crystallin



doi:10.1016/j.jmb.2004.08.050 J. Mol. Biol. (2004) 343, 435–444

JMB

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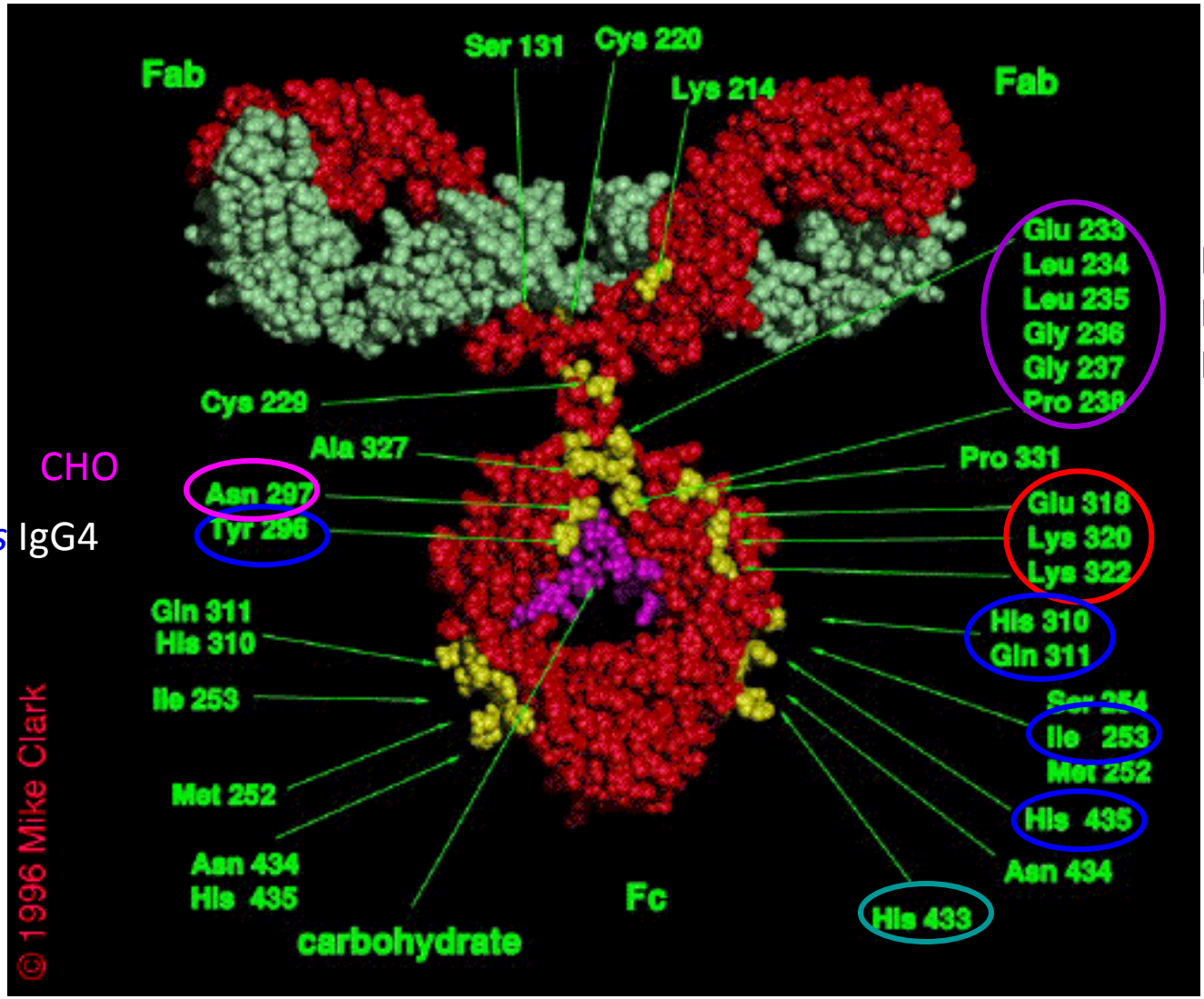
The P23T Cataract Mutation Causes Loss of Solubility of Folded γD-Crystallin

P. Evans[1], K. Wyatt[2], G. J. Wistow[2], O. A. Bateman[1], B. A. Wallace[1,3] and C. Slingsby[1]*

[1]*Department of Crystallography, Birkbeck College, Malet Street, London WC1E 7HX, UK*

Mutations in the human γD-crystallin gene have been linked to several types of congenital cataracts. In particular, the Pro23 to Thr (P23T) mutation of human γD crystallin has been linked to cerulean, lamellar, coralliform, and fasciculiform congenital cataracts. We have expressed and purified

We know a lot about the roles of various amino acid residues in antibody function



Mike Clark Chem. Imm. 1997 and http://www.path.cam.ac.uk/~mrc7/mikeimages.html

How to *demonstrate* if small differences are clinically meaningful or not?

Differences that *might* impact clinical performance will need to be evaluated through analysis of biological activity & possible impact on PK.

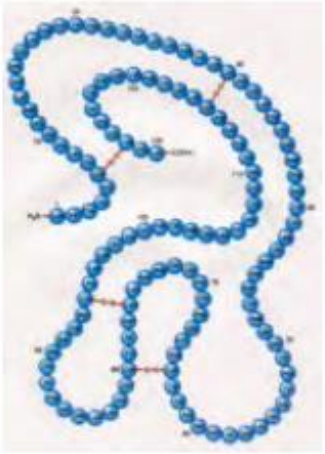
How good do the analytics need to be?

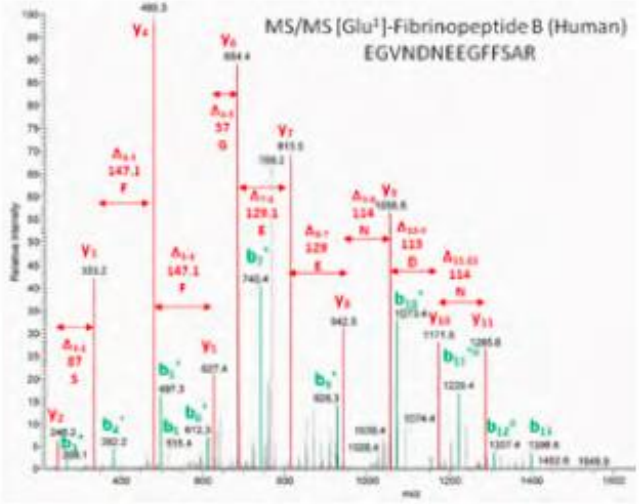
State-of-the-Art

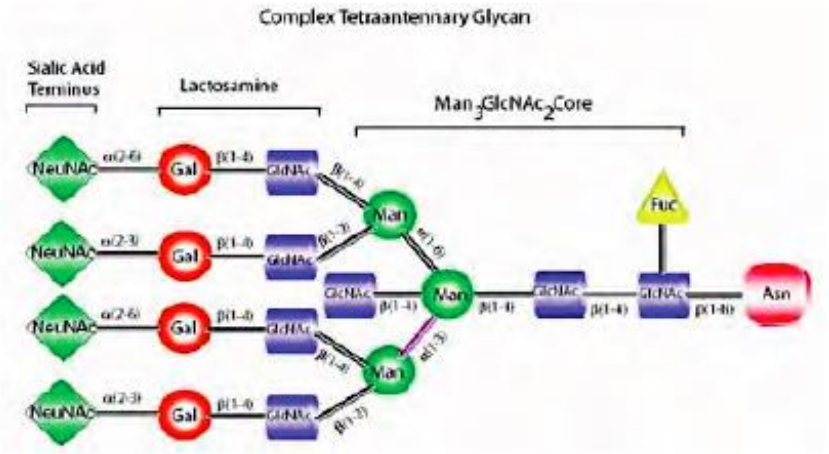
Able to detect and characterize major & minor molecular differences between products

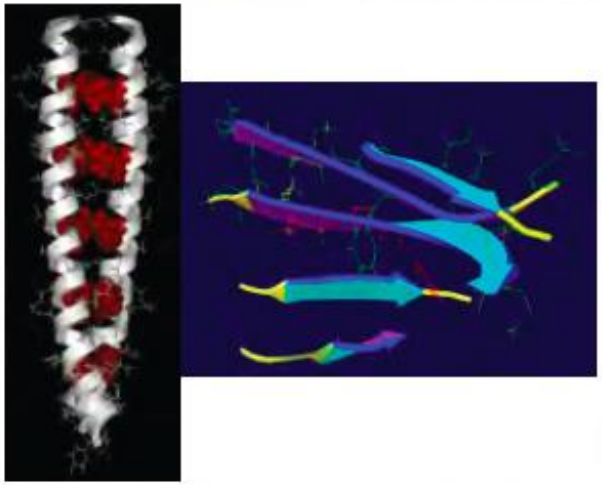
Analytical Tools: State-of-the-Art?

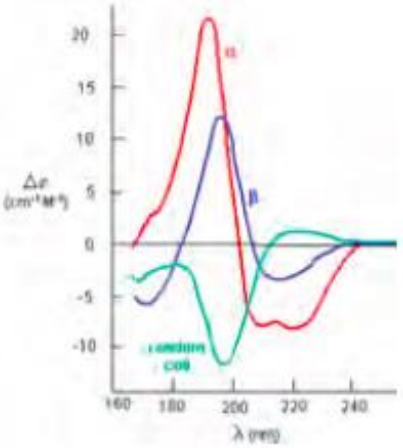
Users of Blunt Tools Need not Apply

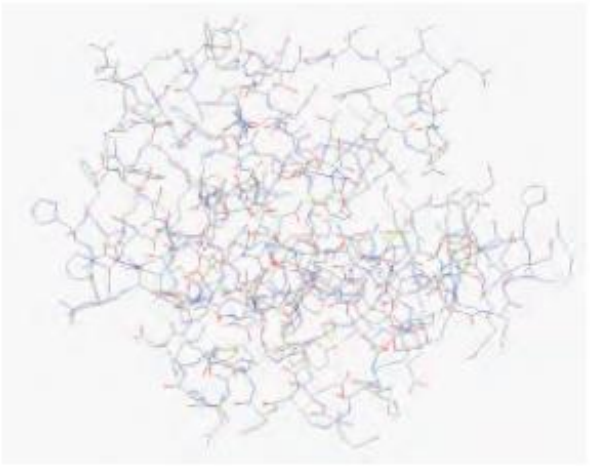


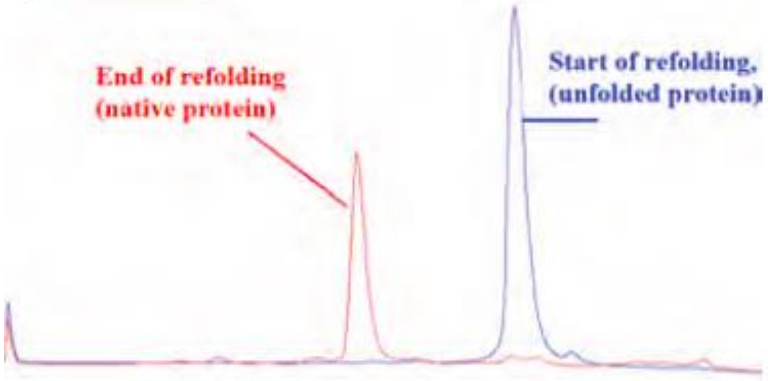

MS/MS [Glu¹]-Fibrinopeptide B (Human)
EGVNDNEEGFFSAR

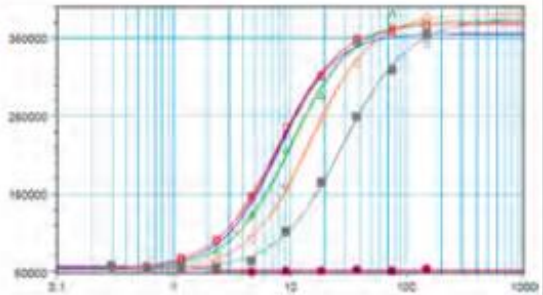

Complex Tetraantennary Glycan
Sialic Acid Terminus
Lactosamine
Man3GlcNAc2Core
NeuNAc
Gal
GlcNAc
Man
Fuc
Asn

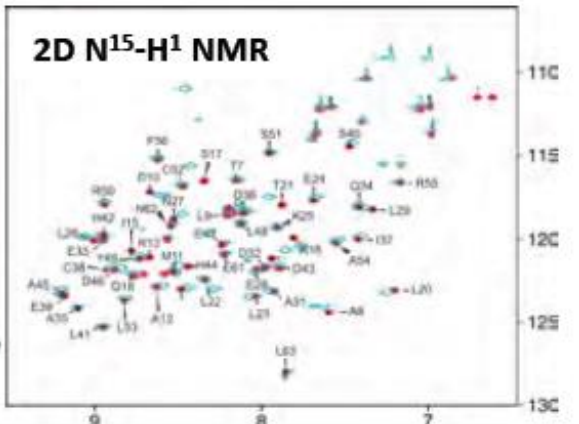



Δε (cm⁻¹M⁻¹)
λ (nm)




End of refolding
(native protein)
Start of refolding,
(unfolded protein)




2D N15-H1 NMR

Comprehensive Similarity Assessment

- **Deep analysis and comparison to multiple lots of US-licensed Reference Product collected over years**
- **Orthogonal, state-of-the-art analytical methods**
- **Stress testing to make sure no hidden difference missed**
- **Latest paradigms for sensitive clinical pharmacology studies**

Modern Similarity Assessment

Old stories on how adverse events arose from undetected product differences following manufacturing changes (*e.g.*, Eprex) unlikely to play out today because of

(a) Better analytics

(b) Extended use of those analytics

What causes immunogenicity to a protein product?

- **Amino acid sequence & modifications**
- **Folded structure**
- **Size (*e.g.*, protein aggregates)**
- **Impurities (*e.g.*, leachables)**
- **Route & Location of Administration**
- **Dosing scheme (chronic, acute)**
- **Immune status of patient (cancer *vs* chronic inflammatory disease)**

Potential risks of immunogenicity to a protein product

- **Loss of efficacy**
- **Deficiency syndrome**
  (non-redundant physiological pathway; *e.g.*, Epo, TPO)
- **Hypersensitivity reaction**
- **Change in PK**

Most licensed protein products have *some* level of immunogenicity

Few are associated with safety issues

Evaluate the risks product-by-product

Comprehensive Similarity Assessment

FDA-approved biosimilars will be among the most deeply analyzed & predictable products to hit the market, in excess of most low molecular weight generics (perhaps except enoxaparin).

Will they be Interchangeable? tbd by FDA

Special thanks to:

My former co-workers in the

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CDER/FDA

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Takoma Park, MD