

Follow-on Protein Products: Comparability and Risk

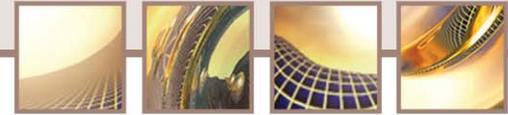
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“Promoting Affordable Biologics”

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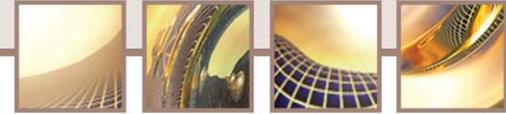
Washington, DC



Recombinant Therapeutic Proteins

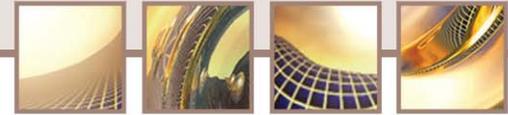
- 51 Federal Register, p 23309 (June 26, 1986): “New license applications or new drug applications are required before marketing products made with recombinant DNA technology, even if the active ingredient in the product is thought to be identical in molecular structure to a naturally occurring substance or a previously approved product produced in an established manner.”

- ***Approved*** or ***Licensed*** under two different statutes
 - Federal Food, Drug, and Cosmetic Act (Section 505)
 - Public Health Service Act (Section 351)



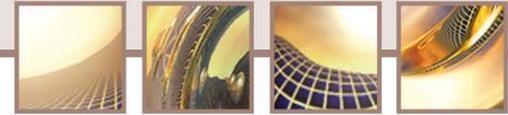
FD&C Act: NDA Pathway

- Therapeutic Biotech products approved under the FD&C Act (NDA) include:
 - Hormones (insulin, growth hormone, FSH, LH, calcitonin, etc.)
 - Enzymes (Cerezyme)
 - Anticoagulant (e.g., PEG-Hirudin)



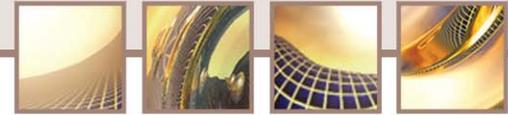
PHS Act: BLA Pathway

- Therapeutic biotech products licensed under the PHS Act include:
 - Interferons
 - G-CSF
 - EPO
 - t-PA
 - Monoclonal Antibodies
- Other products licensed under the PHS Act
 - Blood Products
 - Vaccines and allergenic products
 - Cell and gene therapies



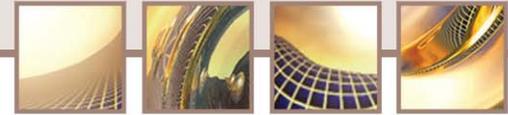
The Biologics License Application

- Section 351 of the PHS Act and regulations at 21CFR 601.2 provide the basis for licensure.
 - “The Secretary shall approve a biologics license application on the basis of a demonstration that: (i) the biological product that is the subject of the application is safe, pure, and potent; and (ii) the facility in which the biological product is manufactured, processed, packed, or held meets standards assigned to assure that the biological product continues to be safe, pure, and potent.” [PHS Act]
 - “... shall submit data from non-clinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency.” [21 CFR]



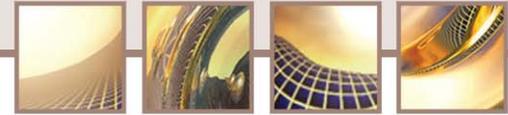
Traditional Biological Products

- Although exceptions existed, biologics were complex molecular mixtures that were, at best, only partially amenable to structural characterization.
- Assurance of product comparability on a lot-to-lot basis was based primarily on the exact repeatability of the manufacturing process [if each step in the manufacturing process is repeated identically, an identical end product will result]. Hence, the paradigm,
 - *“The Product is the Process.”*
- Equating the product with the process serves as a barrier to process changes; essentially, process changes require clinical trials to demonstrate product comparability



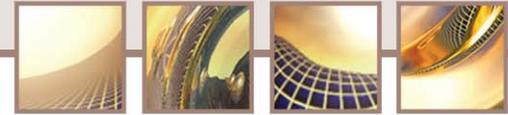
rDNA Biological Products

- Recombinant proteins, in contrast to traditional biological products, were highly pure and were, to a significant degree, amenable to characterization at the molecular level.
 - Microheterogeneity, however, recognized as an issue
- As a consequence, the manner in which these “well-characterized” biologicals were regulated changed.
- This included changes in the licensing application, lot-release requirements, and the basis for the implementation of post-approval manufacturing changes.



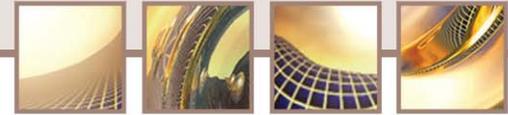
Product Comparability

- Recognizing advances in, *inter alia*, separation sciences and structural characterization methodologies, a pathway to allow process changes to be made without, necessarily, carrying out clinical studies, formalized for specified products
 - *FDA Guidance Concerning Demonstration of Comparability of Human Biologic Products, including Therapeutic Biotechnology-derived Products (April, 1996)*
- Comparability could be established through a combination of analytical and pre-clinical studies; however, if comparability could not be so established, then clinical studies would be needed to validate the process change.



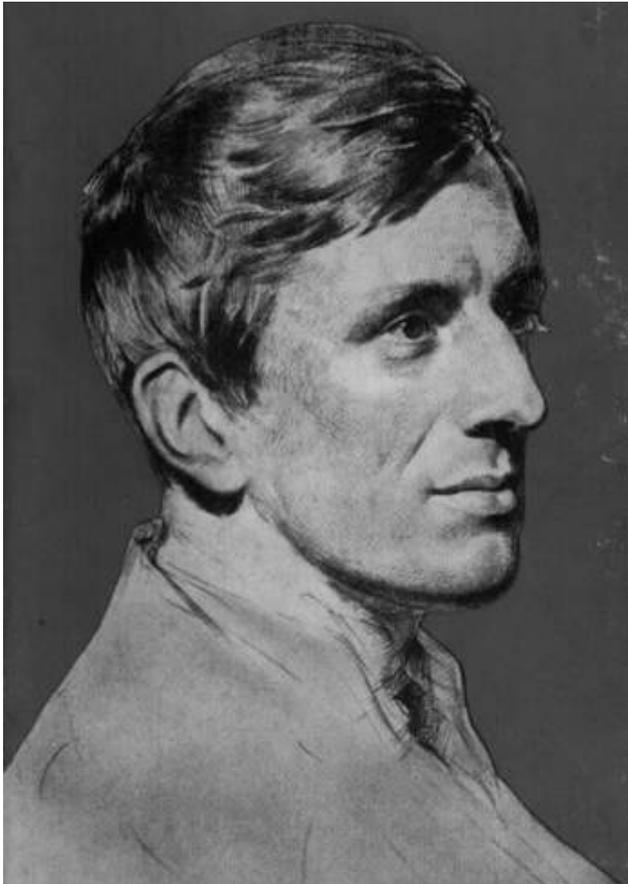
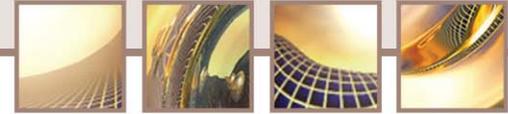
“The demonstration of comparability does not mean that the quality attributes of the pre-change and post-change products are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon the safety or efficacy of the drug product.”

ICH Q5E



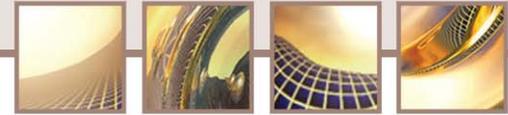
Comparability: Risk and Benefit

- The risk for the implementation of the comparability process is that two products that are deemed to be comparable are not and that there is a risk that a manufacturing change will have an adverse impact on efficacy or safety or both.
- Risks are not taken without reason
- The potential benefits include, as examples:
 - increased purity (potentially safer product)
 - increased yields (increased availability, decreased costs)
 - Improved formulation (greater stability, enhanced safety)



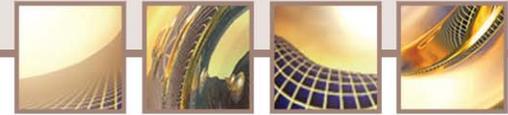
“Nothing would be done at all if one waited until one could do it so well that no one could find fault with it.”

John Henry Cardinal Newman
1801 -1890



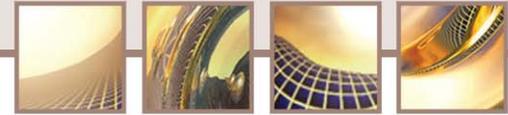
Comparability: Intra-manufacturer

- Highly successful
 - But Eprex is an oft-cited counter-example (but not a good one)
- An ICH document on comparability has been adopted [Q5E]



Extending Comparability: Inter-manufacturer

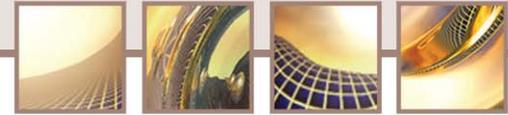
- Can the scientific concepts involved in assessing intra-manufacturer comparability be extended to include comparability of products from different manufacturers?
 - Yes, but we must recognize that molecular complexity is a continuum. The progression from, for example, small to large peptides, to non-post-translationally-modified proteins to post-translationally modified proteins, is one of increasing complexity – but the scientific principles from which comparability is assessed are the same and their application simply dependent on existing knowledge and technology. Increased complexity simply means increased difficulty.
 - FDA is able to evaluate comparability assessments



Berlex Laboratories vs. FDA: Approval of Biogen's Avonex

“FDA's approval of Avonex on May 17, 1996, marked the first time FDA had approved a biological product ... without requiring the completion of full clinical trials on that actual product. In approving Avonex, FDA allowed Biogen to rely on the results of a clinical study of another company's interferon beta product, known as BG9015, after concluding that BG9015 was "comparable" to Avonex.”

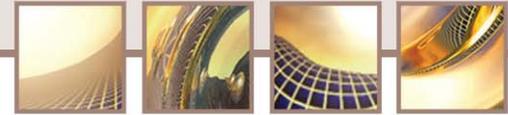
- 942 F. Suppl. 19; U. S. Distr. *LEXIS* 15169 October 7, 1996



Berlex Laboratories vs. FDA Approval of Biogen's Avonex

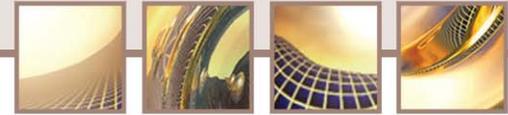
“Neither the PHSA itself nor FDA’s regulations under the PHSA provide that the clinical study offered to demonstrate the safety, purity and potency of a new biological product shall have been conducted on that very product. The absence of a specific opinion on this point raises the now standard question of whether the agency’s view of what is “appropriate in the context of this particular program” is a reasonable one. FDA’s policies and its interpretation of its own regulations will be paid special deference because of the breadth of Congress’ delegation of authority to FDA and because of FDA’s scientific expertise.”

- 942 F. Suppl. 19; U. S. Distr. *LEXIS* 15169 October 7, 1996



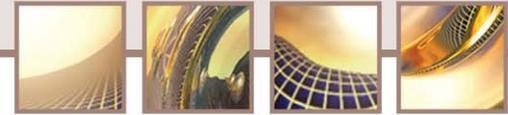
Follow-on Protein Products: What are They?

- The term *follow-on protein products* refers to “proteins and peptides that are intended to be sufficiently similar to a product already approved ... or licensed ... to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product. Follow-on protein products may be produced through biotechnology or derived from natural sources.” [FDA 5/30/06 response the 5/13/04 Citizen’s Petition]
- Interchangeability
 - Is interchangeability a necessary part of the definition?



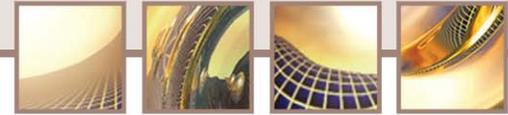
Factors in a Comparability Evaluation

- A comparability evaluation is based on:
 - The ability to characterize the product
 - Chemical characterization
 - Biological characterization
 - Clinical characterization
 - Clinical experience and knowledge of the disease and treatment (a contextual framework for evaluation)
 - Process experience and knowledge



An Evaluation of Comparability: Chemical Characterization

- Ability to separate and quantify individual species or related ensembles of species
 - Product variants and product related impurities
 - Process related impurities
- Ability to characterize individual species
 - Primary and higher order structure
 - Post-translational modifications
 - Degradation products (*e.g.*, oxidation)
- Biological activity of various species



Elements of Protein Structure

■ Primary structure

- Sequential order of amino acids & any chemical modifications (e.g., glycosylation)

■ Secondary Structure

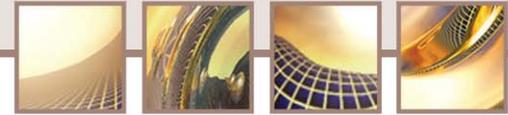
- Describes the locally ordered, three-dimensional structure of the protein (alpha helices, beta sheets, loops/turns)

■ Tertiary structure

- Describes the overall three dimensional structure of the protein (interaction of the secondary structures)

■ Quaternary structure

- Describes the three-dimensional arrangement of protein subunits



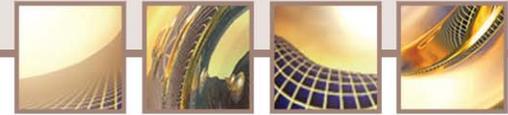
Assessing Protein Structure

■ Primary Structure

- Peptide digests/mass spectrometry

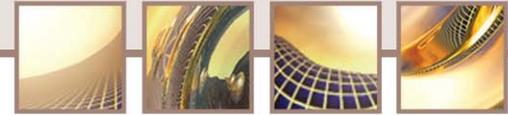
■ Higher order structure

- Circular dichroism
 - Fluorescence spectroscopy
 - FT-IR
 - Amide hydrogen-deuterium exchange
 - Differential scanning calorimetry
 - NMR spectroscopy
 - Laser light scattering
- Higher order structure can be studied as a function of a variety of parameters such as pH, temperature, or added salts to monitor comparability



Separation and Characterization Rapidly Becomes More Complicated

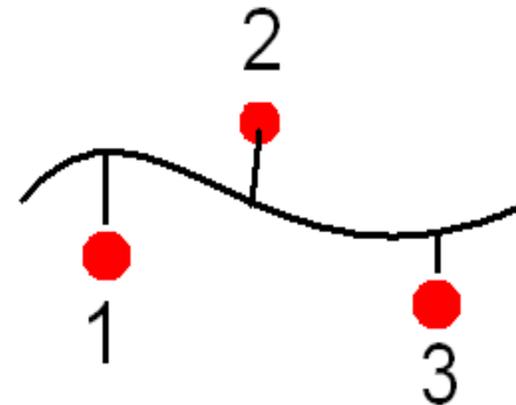
- Molecular Complexity Increases as
 - Overall size of protein increases
 - Number of glycosylation sites increases
 - Number of potential modifying sugars at any site increases
 - Number of other post-translational modifications increases (γ -carboxylation)
 - Consider protein degradants (deamidation, oxidation)
- The *a priori* definition of comparable becomes more difficult as does the demonstration of comparability



A Simple Case: Glycoforms

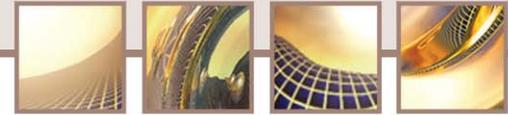
<u>1</u>	<u>2</u>	<u>3</u>	<u>%</u>
-	-	-	a
+	-	-	b
-	+	-	c
-	-	+	d
-	+	+	e
+	-	+	f
+	+	-	g
+	+	+	h

Consider that a given sugar may variably occupy one or more of three sites



2^n Components

$2^n - 1$ Glycoforms



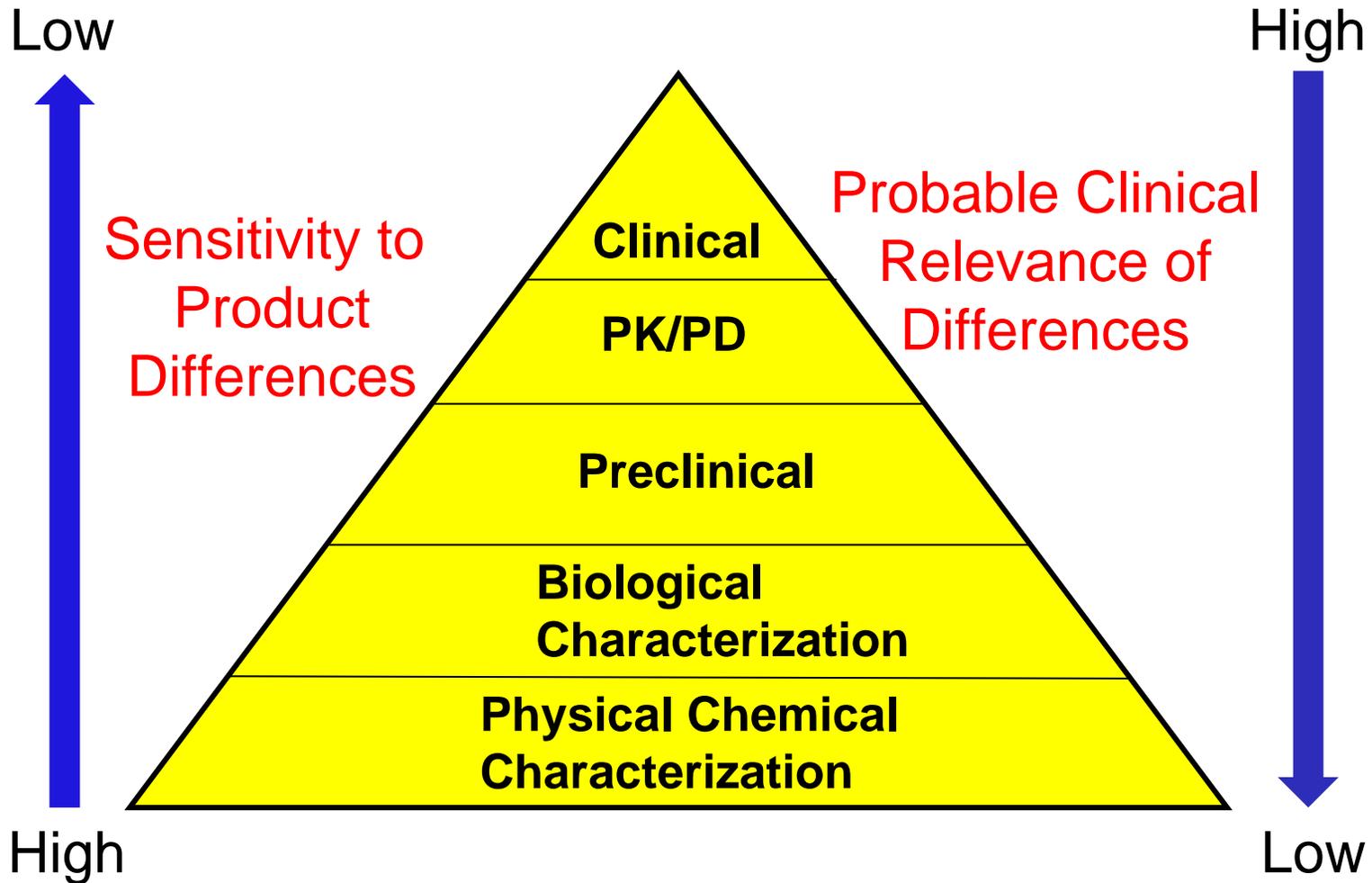
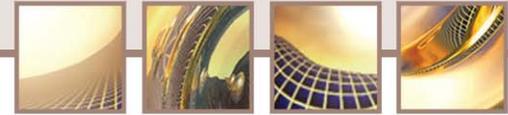
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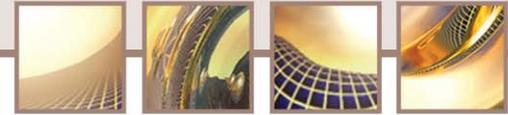
Can determine

<u>1</u>	<u>2</u>	<u>3</u>	<u>%</u>
-	-	-	a
+	-	-	b
-	+	-	c
-	-	+	d
-	+	+	e
+	-	+	f
+	+	-	g
+	+	+	h

1. The overall extent of glycosylation (sugar:protein ratio)
2. The extent of glycosylation at each of the three sites
3. The amount of each species, a – h.

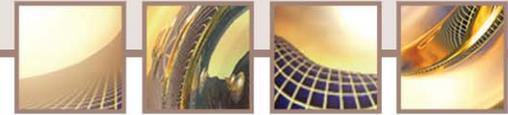
What is necessary to be considered comparable?





An Evaluation of Comparability Clinical Knowledge and Experience

- Extent of use
 - Long or short; broad or narrow
 - Single manufacturer or many manufacturers
- Adverse event history
 - No significant adverse event experience or extensive adverse event experience
 - Adverse events with related products
- Therapeutic index for the product
 - Narrow or wide

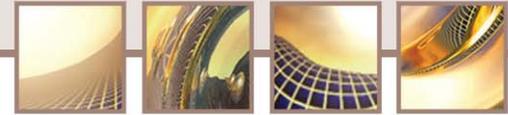


An Evaluation of Comparability Process Knowledge

■ Process knowledge

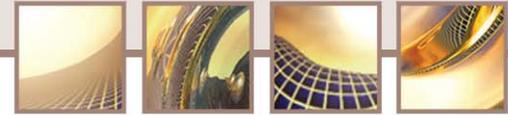
- Potential for various process steps to affect protein quality and in what manner
- Batch to batch variation in the drug product (and clinical consequences)

■ Quality by Design



Comparability and Process Knowledge

- Process knowledge is important for each manufacturer – it provides an assurance of product consistency
- But, is knowledge of another manufacturer's process important for inter-manufacturer comparability assessments?
 - No. Each manufacturer (innovator and follow-on) must have validated manufacturing processes that provide consistent product.
 - There may be more than one pathway to a given product.



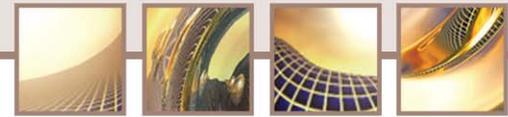
Safety and Efficacy

■ Comparability and efficacy

- A function of the drug substance
- Comparability studies more conducive to establishing efficacy

■ Comparability and safety

- Comparability studies less conducive to establishing safety
- Intrinsic safety profile of the drug substance
 - “Exaggerated pharmacology” [A. S. Lubinecki and M. M. Federici, *Biologicals*, **34**, 45 – 47 (2006)]
- Safety issues associated with process and product impurities
 - Immunogenicity
 - Altered specificity of minor species



Immunogenicity

■ Molecular aggregates

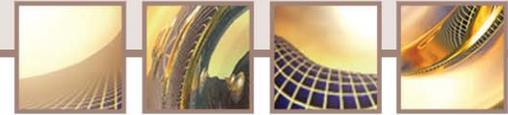
- Susceptibility and microheterogeneity
- Susceptibility and variant forms (e.g., methionine S-oxide)
- A.S. Rosenberg (2006) Effects of Protein Aggregates: An Immunologic Perspective, *The AAPS Journal*

<http://www.aapsj.org/view.asp?art=aapsj080359>

■ Detecting aggregates

- SEC (or FFF) – MALLS
- Analytical ultracentrifugation/sedimentation velocity

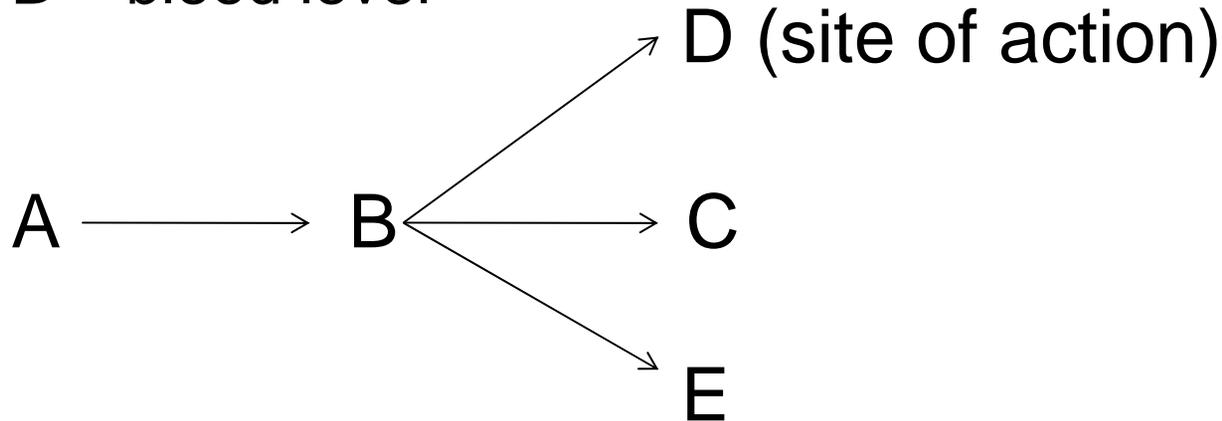
■ Secondary structure changes (e.g., deamidation results in change in protein charge – structural consequences)



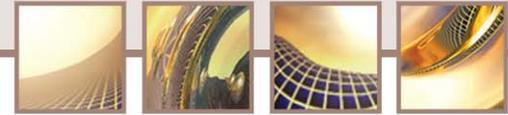
Interchangeability

Pharmacokinetics: Is a similar PK profile sufficient?

B = blood level

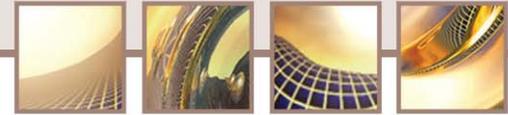


Q. Can products that are not interchangeable be considered comparable?



Orphan Drugs

- “Two protein drugs would be considered the same if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the differences were shown to be clinically superior.” 21 CFR 316.3 (b)(13)(ii)(A)
- Acknowledges that, for example, minor differences in amino acid sequence do not necessarily alter the safety and efficacy of the protein therapeutic.
- Seven years of exclusivity for an orphan drug



Follow-on Protein Products: Summary

- Licensure of Follow-on Protein Products
 - Extension of comparability – science based
 - Evaluations can be made by FDA
- Interchangeability – science based
 - Evaluations can be made by FDA
- Exclusivity period – economics
 - Set by the Congress