Follow-on Biologics: A Brief Overview

Rachel E. Behrman, M.D., M.P.H.
Associate Commissioner for Clinical Programs
Director, Office of Critical Path Programs
November 2008

U.S. Department of Health and Human Services
Food and Drug Administration

A Drug Product —

- As defined in Federal Food, Drug, and Cosmetic Act (FD&C Act):

  articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; articles intended to affect the structure or any function of the body of man or other animals.

A Biological Product —

- As defined in Section 351(i) of the Public Health Service Act (PHS Act):

  "…a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound…)"

Wide Spectrum of Products

- Cells, living tissues, vaccines, blood (all regulated as biological products)
- Proteins
  - Consist of chains of amino acids linked by peptide bonds
  - Range from
    - Simple *to* large and highly complex
    - Highly purified, well characterized synthetic or recombinant *to* relatively crude extract from a human, animal, or plant source
  - May be regulated as biological products or as drugs depending on type of protein and use (and history)

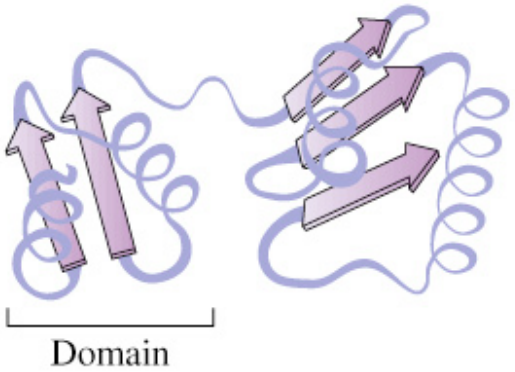
Levels of Protein Structure

–Ala–Glu–Val–Thr–Asp–Pro–Gly–

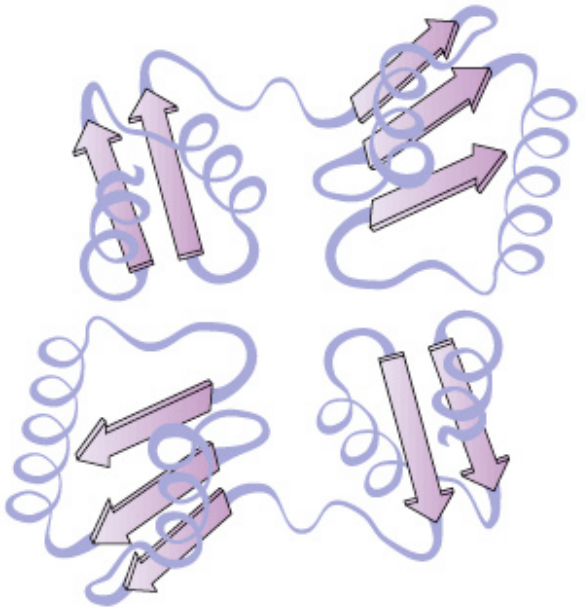
Primary

Secondary

Tertiary



Quaternary



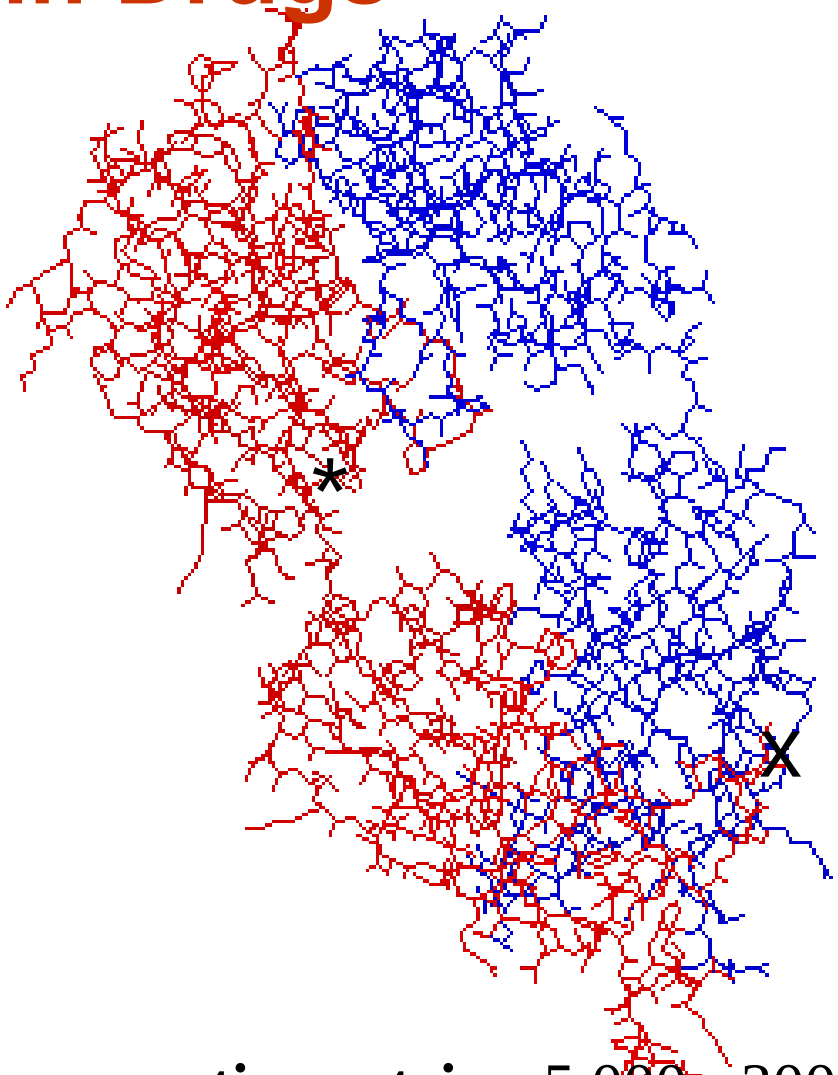
Structure of Small Molecule *vs* Protein Drugs

Proteins have expected:

- Size, charge, hydrophobicity
- Correct folding (S-S bonds)
- Subunits
- Glycosylation
- Bioactivity

& Unexpected:

- Aggregation (side effects)
- Incorrect folding
- Amino acid modifications
  - ox, deam, cyc
- Truncation, proteolysis



Statin

~400 Da

Therapeutic protein ~5,000 - 300,000 Da

Abbreviated Application —

- One that relies, to at least some extent, on the Agency's conclusions about the safety and effectiveness (or safety, purity, and potency) of an approved (or unlicensed) product

- Under the PHS Act – no explicit pathway

- Under the FD&C Act – two pathways
  - 505(j)
  - 505(b)(2)

Terminology

- ***Pharmaceutical Equivalents***

  Drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient or (e.g., for modified release dosage forms) that deliver identical amounts of active drug ingredient over the identical dosing periods 21 CFR 320.1(c)

- ***Bioequivalence***

  The absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action when administered under similar conditions 21 U.S.C. 355(j)(8)

- ***Therapeutic Equivalents***

  Approved drug products that are pharmaceutical equivalents and for which bioequivalence has been demonstrated

  Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered under the conditions specified in the labeling and will receive an "A" equivalence evaluation code in FDA's Orange Book

- ***Substitutable***

  It is FDA's position that products classified as therapeutically equivalent may be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

Other Relevant Terminology

- ***Comparability***

  The comparison by the manufacturer of a biological product before and after a manufacturing change to demonstrate that the safety, identify, purity, and potency remain unchanged http://www.fda.gov/cder/Guidance/compare.htm

- ***Follow-on***

  Informal term, referring to products intended to be sufficiently similar to an approved product to permit an applicant to rely on certain existing scientific knowledge about the safety and effectiveness (or safety, purity, and potency) of the approved product

Potential Regulatory Considerations

- Is the product sufficiently similar to a licensed product to allow reliance on existing scientific knowledge about that product?
- If so, does the Agency have access to those data or to the conclusions about safety and efficacy?
- What additional information is needed to support the claim of “safe, pure and potent”?
- Are there any data provided that would support the safety to “switching”?

Consider the Following

- In most cases, at this time it will be impossible to establish that active ingredients are ***identical*** for follow-on biologics.
- The more complex the product, the more difficult (and expensive) it is to manufacture.
- Concerns about immunogenicity will likely need to be addressed in any follow-on application.
- Review of any application involves making an assessment of what is in the best interest of the public, given available information; uncertainty is almost always involved, as with the approval of any drug or biological product.

Overarching Principle

"The agency has a longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources…and avoiding ethical concerns associated with unnecessary duplication of…human testing."

("FDA's assessment...." In Nature Drug Discovery, 2007)

References

- Janet Woodcock, M.D., Statement before the Committee on Oversight and Government Reform, US House of Representatives http://oversight.house.gov/documents/20070326104056-22106.pdf.
- "FDA's assessment of follow-on protein products: a historical perspective," Nature Reviews Drug Discovery, 2007 Jun (6):437-42.
- U.S. Food and Drug Administration, Guidance for Industry: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998, http://www.fda.gov/cder/guidance/1397fnl.pdf.
- U.S. Food and Drug Administration, Citizen Petition Response - 2004P-0231: Deny Approval of NDA 21-426 for Ominitrop 5.8 mg Somatropin [rDNA origin] for Injection, Lyophilized Powder and Diluent with Preservative, May 30, 2006, http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf.
- "Economic issues with follow-on protein products," Nature Reviews Drug Discovery, 2008 Sept (7):733-37.