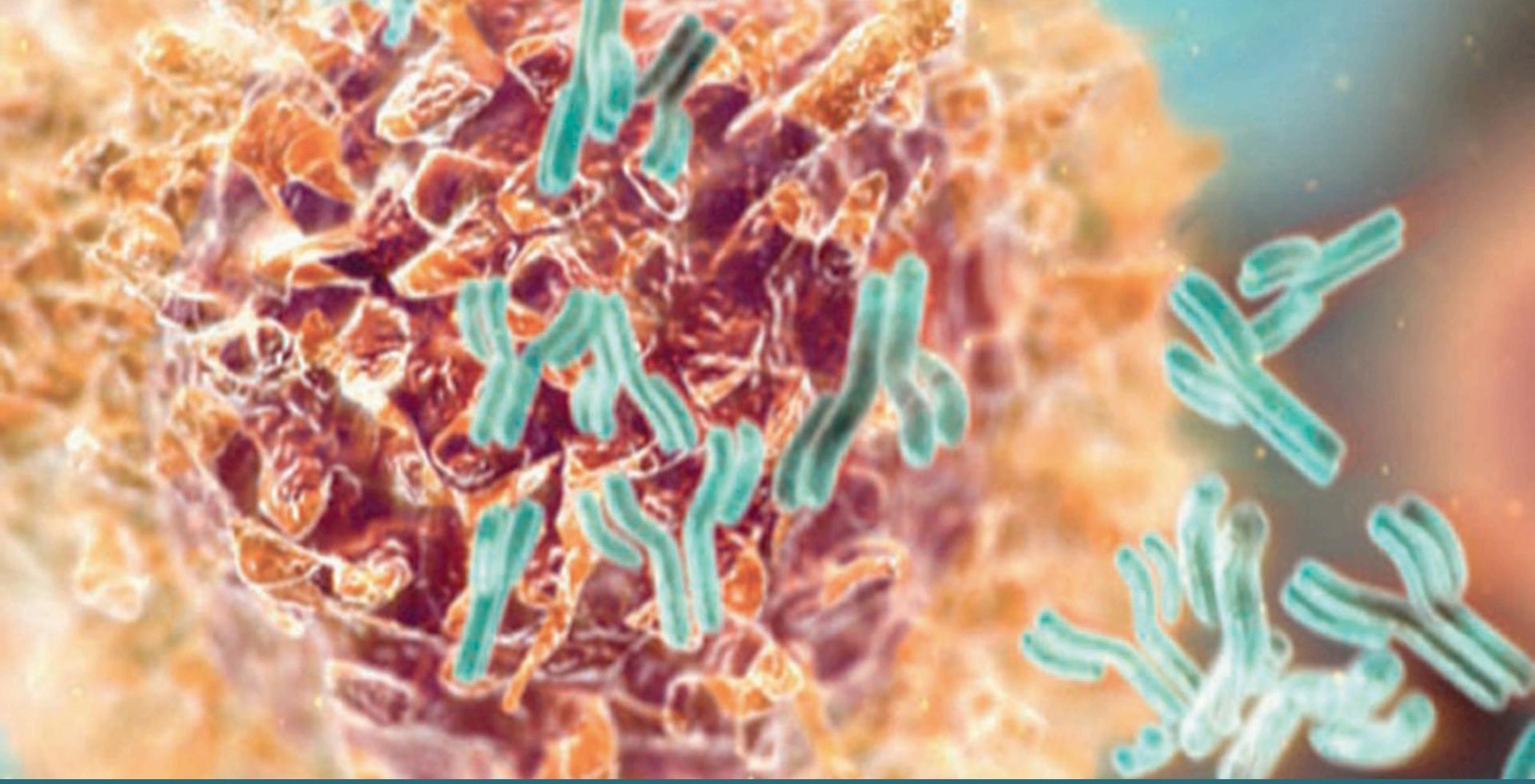


Biosimilars: Regulatory Challenges For The FDA

February 25, 2014

Presented by Dirk Reitsma, MD at the ASBM Forum
Reserve Officers Association Building, Washington, DC

U.S. Biosimilars Policy

Timeline: Creating a U.S. Biosimilars Pathway

March 23, 2010: *Biological Price Competition & Innovation Act (BPCIA)* enacted (as part of the Patient Protection and Affordable Care Act)

- Established a new regulatory pathway for approval of "biosimilars"
- Amended the definition of "biological product" to include "proteins, except chemically synthesized polypeptides"
- Established a 'transition' to begin regulating *all biologicals the same way …including protein products previously approved as "drugs"*
- "Transition" biological products: Human Growth Hormones; Insulins: Hyaluronidase …and others

Biosimilars Policies Under FDA Development

INTERCHANGEABILITY STANDARDS:

- FDA is developing, but has not yet released a draft of standards for *interchangeability* (substitution by a pharmacist, insurer, or other third party)

CLINICAL TRIALS:

- FDA may or may not require for each new proposed biosimilar to demonstrate no new side effects compared with original biologic, which impacts quality & safety

STRUCTURE & FUNCTION OF THE ORIGINAL BIOLOGIC:

- FDA may or may not require a complete scientific evaluation and understanding of the biological product and proposed biosimilars before approval, which impacts quality & safety

Biosimilars Policies Under FDA Development (cont'd)

TRANSITION PRODUCTS POLICY:

- Presumption that FDA uses the same scientific & safety standards regardless of which legal framework was used during transition to approve a "biosimilar"

HOWEVER…

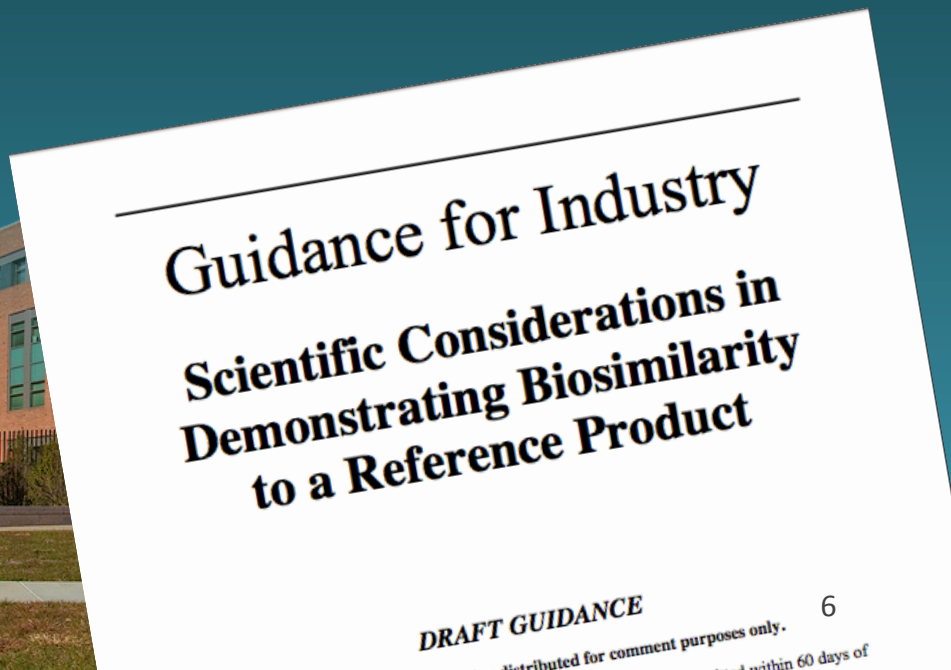
- FDA could approve a "follow on" protein as an "interchangeable" drug based on scientific data that might be insufficient to support a "biosimilarity" or "interchangeability" determination for the same product under the new law after the transition

- Certain "biosimilars" could be approved as "drugs" and substituted or switched at the pharmacy level *without the physicians knowledge* during the transition period that may not otherwise meet new biosimilar interchangeability standards in place for the same product if approved after the transition period.

How is Biosimilarity Defined by Law?

"the biological product is **highly similar** to the reference product, notwithstanding minor differences in clinically inactive component", and "there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product".

-"Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (FDA Draft Guidance, February 2012)



How FDA Will Determine Biosimilarity

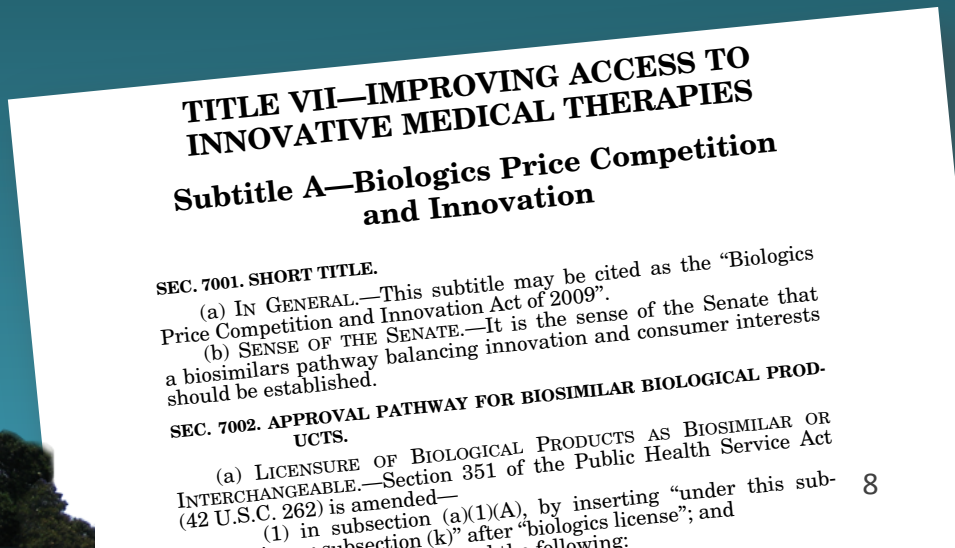
FDA will use the "totality of evidence" to determine "biosimilarity" (same effect without clinically meaningful differences)

- "Stepwise"/sequential approach recommended starting with extensive structural and functional characterization of both the proposed product and the reference product
- Sponsors encouraged to address residual concerns at each step of comparison to determine need for clinical studies & consult extensively with FDA after completion of comparative structural and functional analysis (before finalizing the clinical program)
- FDA will advise on clinical study requirements after review of structural/functional analysis data
- FDA will generally require animal toxicity studies, immunogenicity, PK / PD studies (but FDA could waive or narrow such studies based on analytical data)

How is Interchangeability Defined?

Biologics Price Competition and Innovation Act,
Section (351)(k)(4))

- Be biosimilar to the reference product;
- Be expected to produce the same clinical result as the reference product in any given patient; and
- If the product will be administered more than once to a patient, the risk (in terms of safety or diminished efficacy) associated with switching between the product and the reference product cannot be greater than the risk of repeated use of the reference product.



TITLE VII—IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES

Subtitle A—Biologics Price Competition and Innovation

SEC. 7001. SHORT TITLE.

(a) IN GENERAL.—This subtitle may be cited as the "Biologics Price Competition and Innovation Act of 2009".

(b) SENSE OF THE SENATE.—It is the sense of the Senate that a biosimilars pathway balancing innovation and consumer interests should be established.

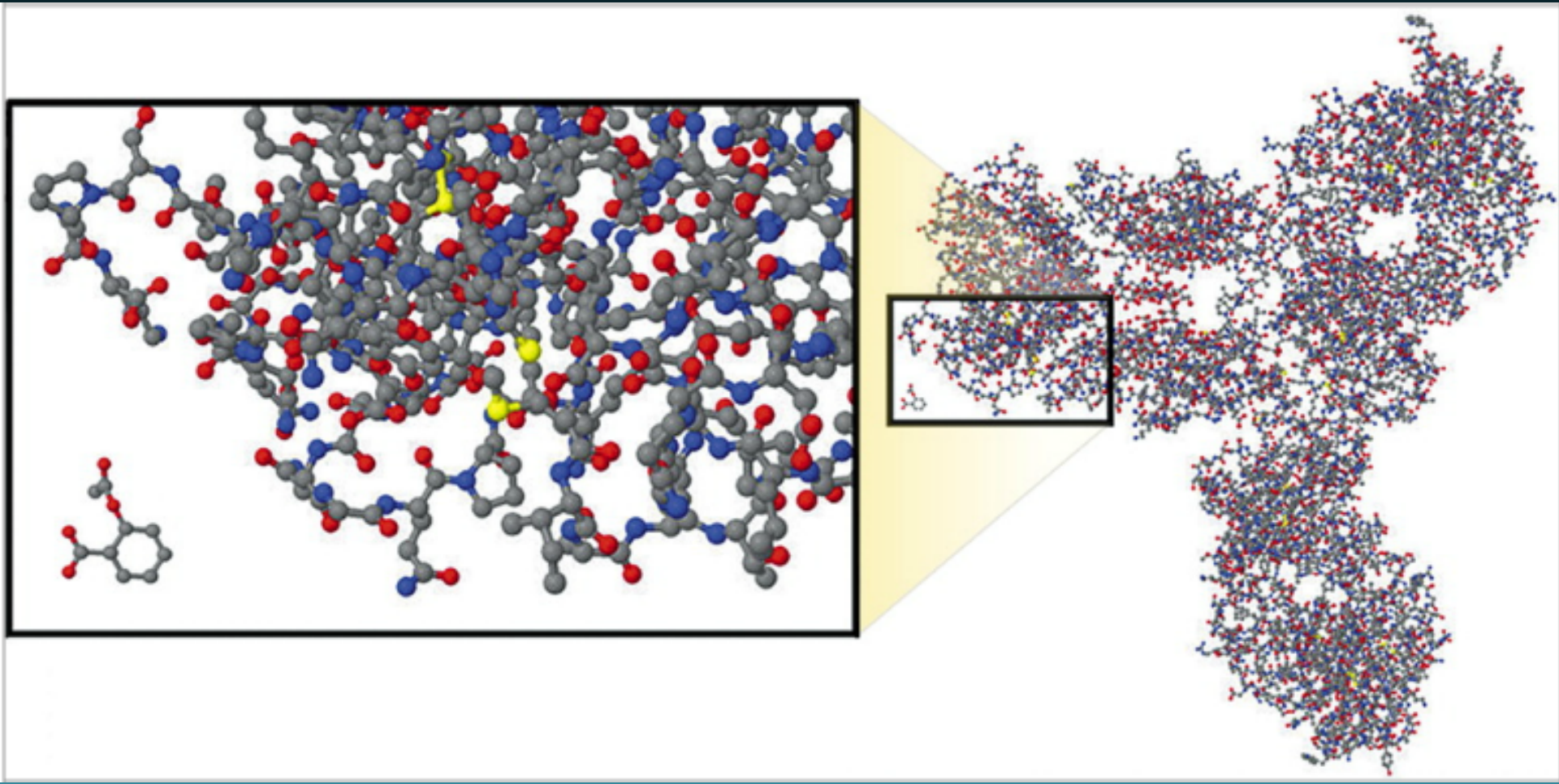
SEC. 7002. APPROVAL PATHWAY FOR BIOSIMILAR BIOLOGICAL PRODUCTS.

(a) LICENSURE OF BIOLOGICAL PRODUCTS AS BIOSIMILAR OR INTERCHANGEABLE.—Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended—

(1) in subsection (a)(1)(A), by inserting "under this subsection (k)" after "biologics license"; and

Determining Interchangeability

The Molecular Complexity of Biologics Makes Interchangeability a Challenging Aspiration



Molecular Comparison: Aspirin vs. Biologic Monoclonal Antibody

Data Requirements

The types of data requirements that are likely to assure the FDA that a biosimilar is interchangeable:

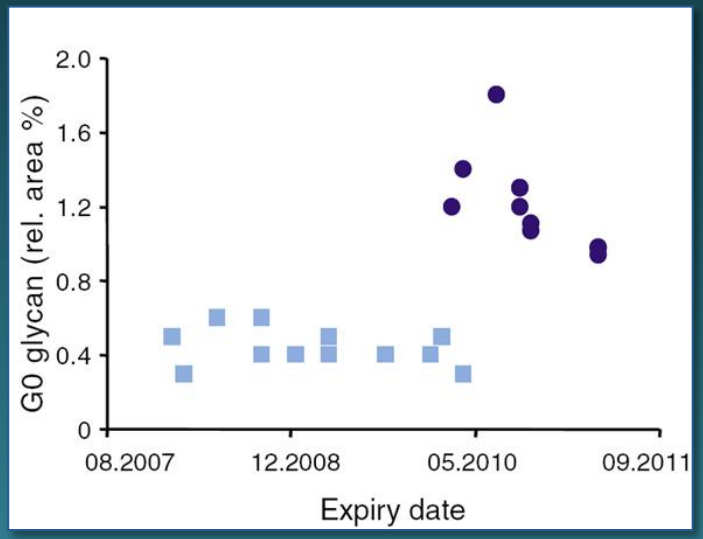
- FDA is still considering the type of information sufficient to enable an interchangeability determination
- FDA can make an interchangeability determination as part of its review of an original biosimilar application following a decision that the product is biosimilar.
- Will be separate standard for interchangeability—FDA has suggested as indicated in the law that there will be a higher bar as part of the two step process
- Clinical studies (beyond PK/PD)/switching trials may be required

Data Requirements (cont'd)

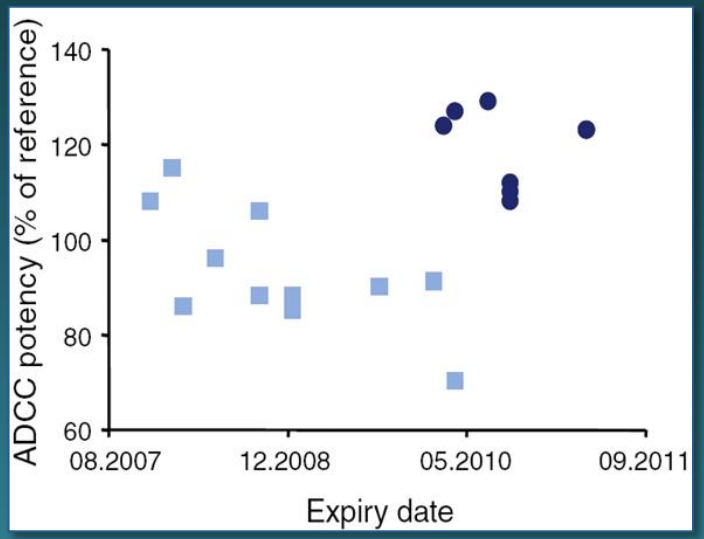
- Sponsors advised to make strategic decision to pursue both biosimilarity and interchangeability vs. just biosimilarity given cost/ timing necessary to demonstrate interchangeability
- Sponsors can submit supplemental application later for interchangeability designation
- Must first have data on comparability demonstrating the biological product is biosimilar to the reference product plus data to demonstrate that the biosimilar can will produce the same clinical result as the reference product in any given patient.
- For a biosimilar administered more than once, the sponsor must also prove that the safety and reduced efficacy risks of alternating or switching are not greater than with repeated use of the reference product without alternating or switching.

Acceptable Changes in Quality Attributes of Rituximab

- Commercial batches were characterized from 2007 to 2011
  - Abrupt change in quality profile in 2008 (expiry dates >2010)
  - Most likely related to a change in the manufacturing process
- No need for change in label



- 3-fold increase in unfucosylated G0 glycans



- Translated into increased ADCC potency

Source: *Nature Biotechnology* 2011;29:310-312.

PK/PD Profiles of Biosimilars

- First generation biosimilars
  - Short half life
  - Single dose PK, PD
  - Cross over feasible

- Monoclonal antibody biosimilars
  - Long half life
  - Sustained blood levels required
  - Washout between doses not feasible

Proposal to test interchangeability

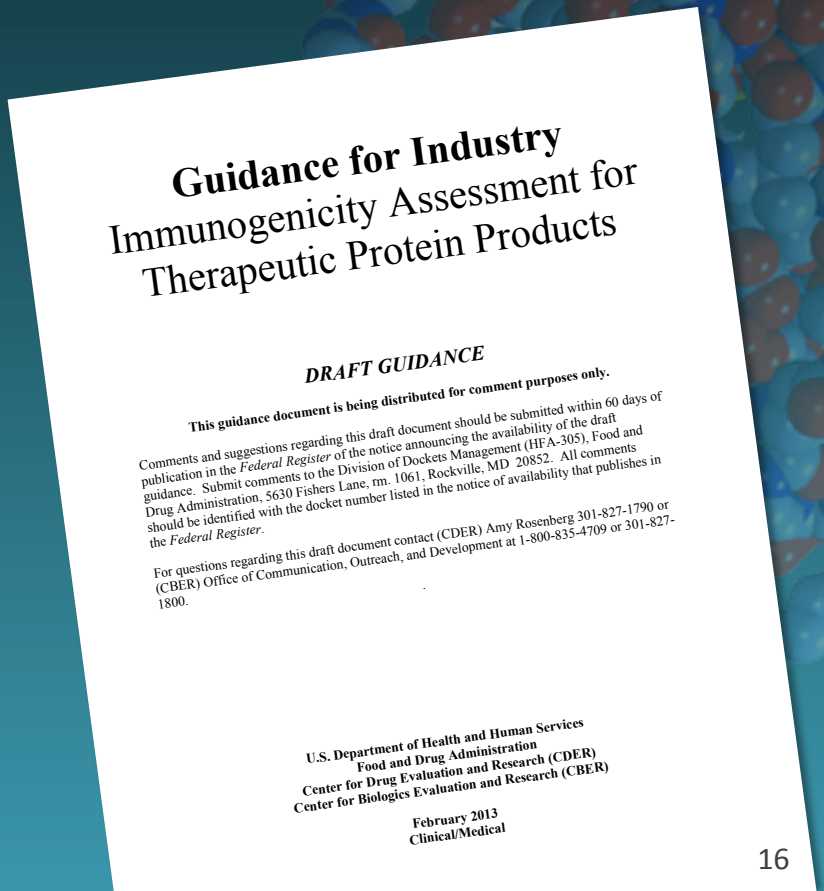
- Four parallel arms
  - Two treatment periods: before and after cross over point
- Biosimilarity comparison
  - R → R
  - B → B
- Interchangeability comparison
  - R → B
  - B → R
- Cross over point
  - One or more than one? When?
  - Acute and chronic safety; efficacy; immunogenicity

One Area Needing to Be Addressed: Immunogenicity

FDA released draft guidance February 2013, saying:

"Immune responses to therapeutic protein products may pose problems for both patient safety and product efficacy. [Immunological adverse events] have caused sponsors to terminate the development of therapeutic protein products or limited the use of what might otherwise be effective therapies."

-FDA Center for Drug Evaluation and Research, in-PharmaTechnologist.com, 2/25/2013



Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Amy Rosenberg 301-827-1790 or (CBER) Office of Communication, Outreach, and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2013
Clinical/Medical

How Biosimilar Approval in the EU and Other Jurisdictions Will Affect the FDA Approval Process.

- Biosimilars will need to go through the FDA approval process in the US to be marketed in the US. The FDA is not required to adopt ex-US policies and often does not, so **that is not a reliable strategy for product development in the absence of further FDA guidance**

- Sponsor may use animal study/clinical data comparing its proposed biosimilar product to a non-U.S.-licensed product but must provide sufficient data to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product (e.g., FDA likely would require a clinical PK and/or PD study conducted with the U.S.-licensed reference product).

Thank you for your attention!

Dirk Reitsma, MD