FDA Immunogenicity Updates

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Overview

- Biosimilars update
- Immunogenicity of Biosimilars – FDA Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2015)
- Zarxio case study

Biosimilars

- To date
  - FDA approved one 351(k) BLA for a biosimilar product, Zarxio (filgrastim-sndz).
  - There are four companies that publicly announced they submitted a total of five applications (351(k) BLAs)
- As of July 31, 2015, 57 programs were in the Biosimilar Product Development (BPD) program for 16 different reference products.
- An additional 27 programs have had an initial advisory meeting with FDA

Biosimilars

- On April 28, FDA published the following final guidances:
  - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
  - Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product
  - Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

Biosimilars

- FDA previously published the following draft guidances:
  - Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants
  - Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009
  - Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
  - Reference Product Exclusivity for Biological Products Filed Under Section 351 (a) of the PHS Act
  - Nonproprietary Naming for Biological Products

Biosimilars

- FDA expects to issue the following draft guidances in 2015 as reflected on the CDER Guidance Agenda:
  - Considerations in Demonstrating Interchangeability to a Reference Product
  - Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity
  - Labeling for Biosimilar Biological Products

Definition of Biosimilarity

Biosimilar or Biosimilarity means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; **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.

Reference Product means the single biological product licensed under 351(a) of the PHS Act

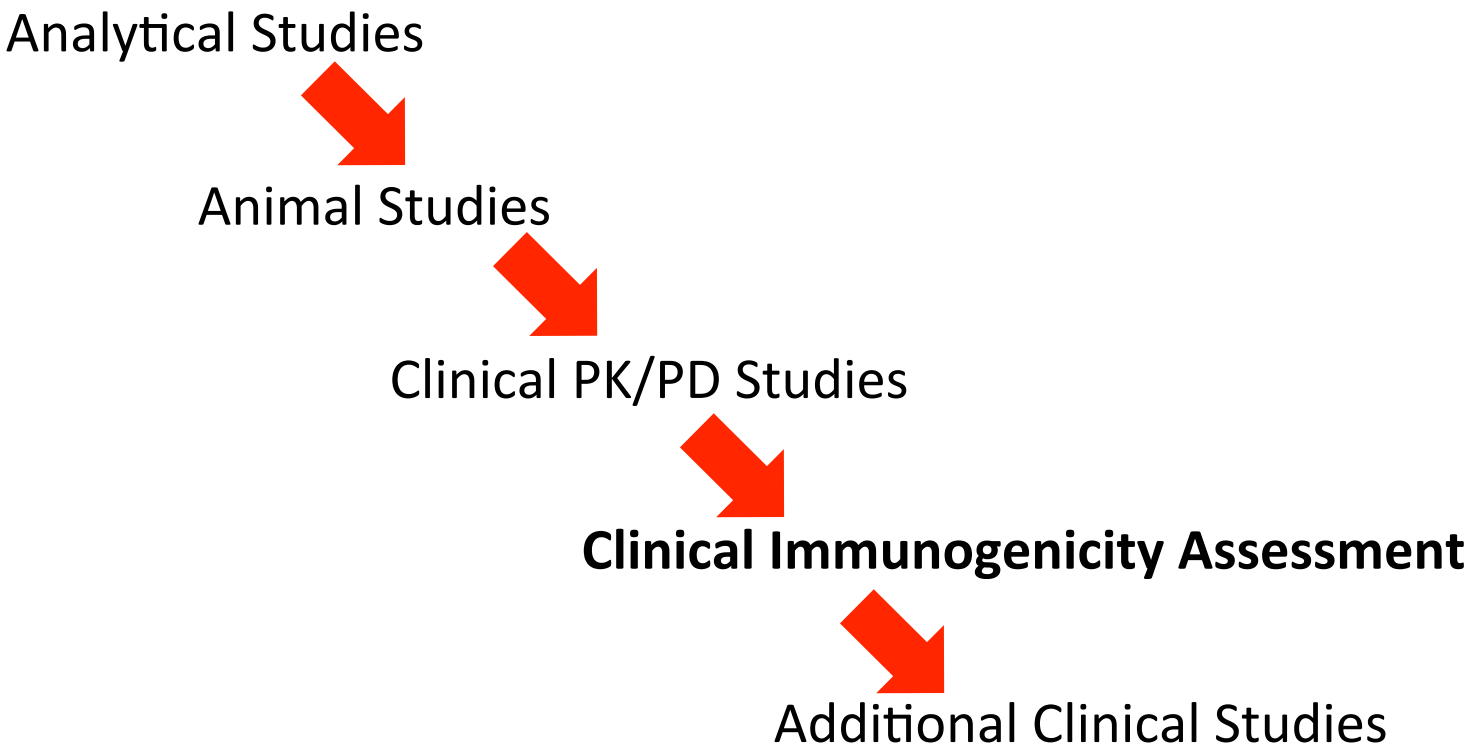
Section 7002(b)(2) of the Affordable Care Act, amending section 351(i) of the PHS Act.

FDA Approach to Assess the Demonstration of Biosimilarity

FDA intends to consider the **totality of the evidence** provided by a sponsor and recommends a **stepwise approach to demonstrating biosimilarity**, which can include a comparison of the proposed biosimilar product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness.

Product Development

Apply a step-wise approach to data generation and the evaluation of residual uncertainty*



* The list is not intended to imply that all types of data described here are necessary for any given biosimilar development program. FDA may determine, in its discretion, that certain studies are unnecessary in a 351(k) application.

Immunogenicity Assessment for Biosimilars

- Interpreting animal immunogenicity results
  - Animal immunogenicity assessments assist in interpreting animal study results
  - Generally do not predict potential immune responses in humans
  - May provide useful information when there are manufacturing differences between the proposed and reference products differences in immunogenicity
  - Differences observed in animal immunogenicity assessments may reflect structural or functional differences not captured by other analytical methods

Immunogenicity Assessment for Biosimilars

- Clinical immunogenicity assessment
  - The nature and scope will depend on the nature and extent of residual uncertainty about biosimilarity after conducting structural and functional characterization and, where relevant, animal studies
  - FDA encourages that, where feasible, sponsors collect immunogenicity data in any clinical study, including human PK or PD studies

Immunogenicity Assessment for Biosimilars

- The scope of the clinical program and the type of clinical studies should be scientifically justified by the sponsor
  - FDA expects a sponsor to conduct comparative human PK and PD studies (if there is a relevant PD measure(s)) and a clinical immunogenicity assessment

Immunogenicity Assessment for Biosimilars

- The scope of the clinical program and the type of clinical studies should be scientifically justified by the sponsor
  - In certain cases, establishing PK, PD, **and immunogenicity** profile may provide sufficient clinical data to support a conclusion of no clinically meaningful differences between the two products
  - However, if residual uncertainty about biosimilarity remains after conducting these studies, an additional comparative clinical study or studies would be needed to further evaluate whether there are clinically meaningful differences between the two products

Immunogenicity Assessment for Biosimilars

- The goal of the clinical immunogenicity assessment is to evaluate potential differences between the proposed product and the reference product in the incidence and severity of human immune responses
  - Effect on safety and effectiveness e.g. altering PK, inducing anaphylaxis, development of neutralizing antibodies that neutralize the product as well as it's endogenous counterpart

Immunogenicity Assessment for Biosimilars

- Structural, functional, and animal data are generally not adequate to predict immunogenicity in humans
- At least one clinical study that includes a **comparison of the immunogenicity** of the proposed product to that of the reference product will be expected

Immunogenicity Assessment for Biosimilars

- The extent and timing of the clinical immunogenicity assessment will vary depending on a range of factors including
  - The extent of analytical similarity between the proposed product and the reference product
  - The incidence and clinical consequences of immune responses for the reference product

Immunogenicity Assessment for Biosimilars

- Considerations for the immunogenicity assessment
  - the nature of the immune response (e.g., anaphylaxis, neutralizing antibody)
  - the clinical relevance and severity of consequences (e.g., loss of efficacy of life-saving therapeutic and other adverse effects)
  - the incidence of immune responses
  - the population being studied

Immunogenicity Assessment for Biosimilars

- Considerations for the study design
  - FDA recommends using **comparative parallel design** (i.e., a head-to-head study) in treatment-naïve patients as the most sensitive design for a premarketing study
  - a sponsor may need to evaluate a subset of patients to provide an assessment of whether a single cross-over from the reference product to the proposed biosimilar would result in a major risk
    - Hypersensitivity
    - Immunogenicity
    - Other reactions

Immunogenicity Assessment for Biosimilars

- Considerations for the study design
  - The design of any study to assess immunogenicity and acceptable differences in the incidence and other parameters of immune response should be discussed with FDA before initiating the study.
  - Differences in immune responses between a proposed product and the reference product in the absence of observed clinical sequelae may be of concern and may warrant further evaluation (e.g., extended period of follow-up evaluation)

Immunogenicity Assessment for Biosimilars

- Considerations for the study design
  - Sponsors should justify the study population used to compare immunogenicity
  - Sponsors should obtain agreement from FDA on these criteria before initiating the study

Immunogenicity Assessment for Biosimilars

- Considerations for the study design
  - To extrapolate immunogenicity findings for one condition of use to other conditions of use
    - Sponsors should consider using a study population and treatment regimen that are adequately sensitive for predicting a difference across the conditions of use.
    - Usually, this will be the population and regimen for the reference product for which development of immune responses with adverse outcomes is most likely to occur

Immunogenicity Assessment for Biosimilars

- Considerations for the study design
  - Immunogenicity issues with the reference product should be considered when selecting clinical immunogenicity endpoints or PD measures associated with immune responses to therapeutic protein products e.g.
    - Antibody formation
    - Cytokine levels

Immunogenicity Assessment for Biosimilars

- Considerations for the study design
  - Sponsors should prospectively define the clinical immune response criteria (e.g., definitions of significant clinical events such as anaphylaxis),
  - For each type of potential immune response sponsors should use established criteria where available
  - Sponsors should obtain agreement from FDA on these criteria before initiating the study

Immunogenicity Assessment for Biosimilars

- Considerations for the study design
  - The duration of follow-up evaluation should be determined based on
    - the time course for the generation of immune responses and expected clinical sequelae
    - the time course of disappearance of the immune responses and clinical sequelae following cessation of therapy, and
    - the length of administration of the product
  - For example, for chronically administered agents, the follow-up period is recommended to be 1 year unless a shorter duration can be scientifically justified based on the *totality of the evidence* to support biosimilarity

Immunogenicity Assessment for Biosimilars

- Considerations for antibody parameters assessed
  - Titer
  - Specificity
  - Relevant isotype distribution
  - Time course of development
  - Persistence, disappearance
  - Impact on PK
  - Association with clinical sequelae
  - Neutralization capacity to all relevant functions (e.g., uptake and catalytic activity, neutralization for replacement enzyme therapeutics)

Immunogenicity Assessment for Biosimilars

- Considerations for immunogenicity Assays
  - The proposed product and the reference product should be assessed in the same assay with the same patient sera whenever possible.
  - Immunogenicity assays should be developed and validated early in development
  - The validation should consider both the proposed product and the reference product

Immunogenicity Assessment for Biosimilars

- Immunogenicity Assays
  - Assays should be capable of sensitively detecting immune responses, even in the presence of the circulating drug product
  - Sponsors should consult with FDA on the sufficiency of assays before initiating any clinical immunogenicity assessment

*EP2006 Immunogenicity Data

Faruk Sheikh, Ph.D, Staff Fellow,
Frederick Mills, Ph.D., Biologist,
Susan Kirshner, Ph.D., Review Chief
OBP

Immunogenicity testing for biologics

- Treatment with therapeutic biological products can cause patients to develop anti-drug antibodies (ADAs)

- ADAs can have severe consequences including:
  - loss of activity of endogenous counterparts
  - hypersensitivity reactions including anaphylaxis
  - loss of efficacy.

- Establishing similarity in the immunogenicity profiles of the proposed biosimilar and the reference product may be an important component of the totality of the evidence supporting the demonstration of biosimilarity.

Immunogenicity of GCSF Products:

- 5 year National Marrow Donor Program publication**
  - Evaluated 6,768 healthy peripheral blood stem cell (PBSC) donors exposed to GCSF and 2,726 healthy bone marrow (BM) donors not exposed to GCSF
  - There was no increased risk for developing an autoimmune disease in PBSC donors when compared to BM donors

**Pulsipher MA, Chitphakdithai P, Logan BR et al. Lower risk for serious adverse events and no increased risk for cancer after PBSCs BM donation. Blood: 123:3655, 2014

Immunogenicity of GCSF Products:

- FDA is unaware of reports of neutralizing ADA to GCSF products.
- The literature indicates that GCSF products are low risk for ADA related severe adverse events.

*Pulsipher MA, Chitphakdithai P, Logan BR et al. Lower risk for serious adverse events and no increased risk for cancer after PBSCs BM donation. Blood: 123:3655, 2014

EP2006 Immunogenicity and Similarity:

- One multi-dose parallel arm study in 214 patients with cancer. No patients developed ADA during the study

- Four single and multi-dose cross-over PK and PD studies in healthy subjects. No subjects developed ADA during the study.

- One single arm multi-dose study of EP2006 in patients with cancer. No patients developed ADA during the study.

Summary:

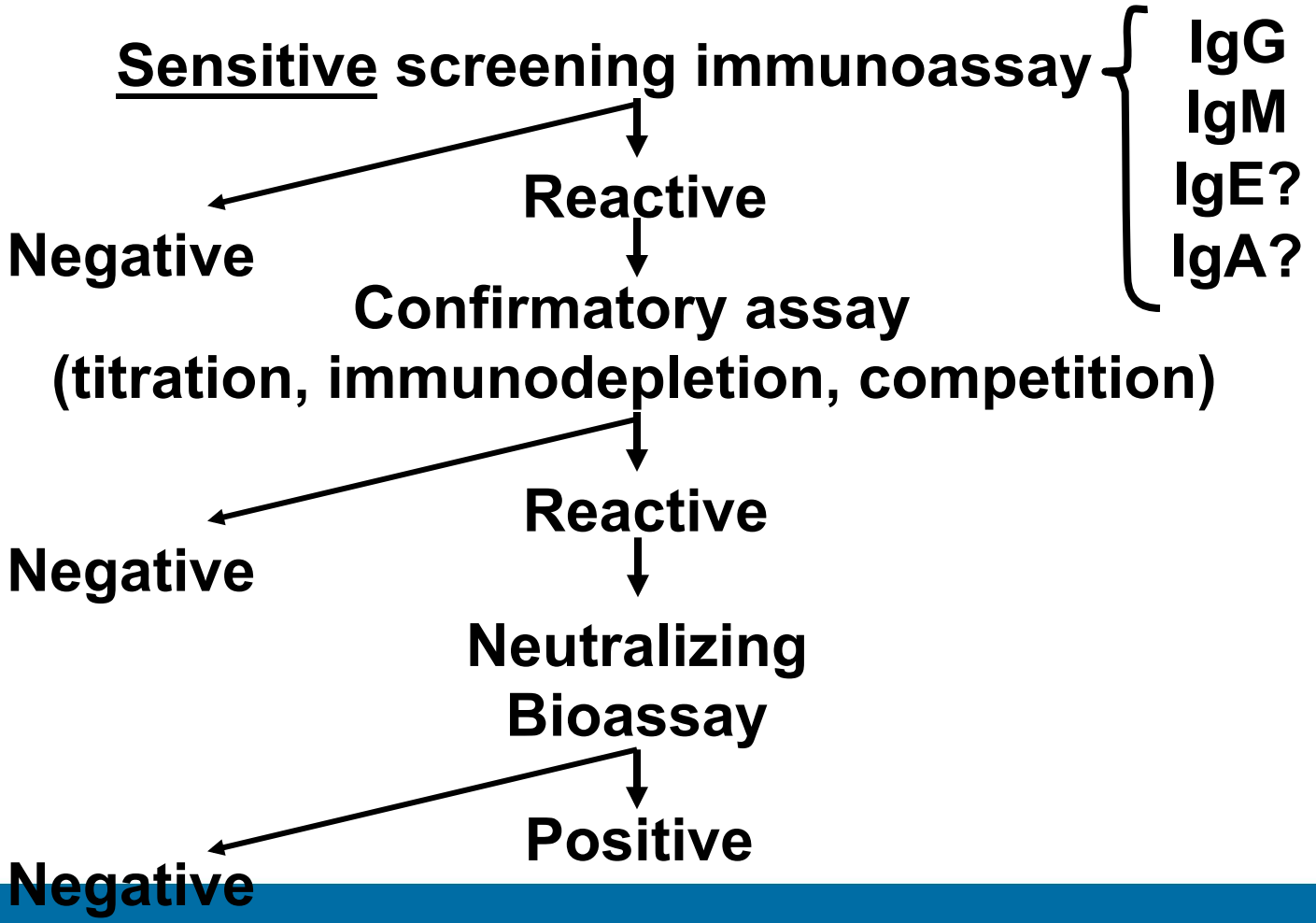
- The results from immunogenicity studies support a demonstration of no clinically meaningful differences in immune response between EP2006 and US-licensed Neupogen.

Immunogenicity Assessment Challenges: Case Study

Immunogenicity Risk Assessment

- Severity of the consequences of ADA
  - Products are considered high risk whenever the consequences of ADA are severe (e.g. PRCA, thrombocytopenia with PEG-MGDF)
- Incidence (occurrence) of ADA
- Detectability of ADA

Evaluating Immunogenicity: A Tiered Approach



Immunogenicity Assay Validation

- Assays are validated for
  - Cut point
  - Sensitivity
  - Specificity and selectivity
  - Precision
  - Reproducibility
  - Robustness

Assay Cut Points

- The cut point of the assay is the level of response which when crossed defines the sample response as positive or negative.
- Correctly establishing the assay's cut point is critical to suitable clinical performance.
- The false negative rate is hard to estimate for ADA assays. Therefore, FDA recommends using a relatively high false positive rate of 5% for the screening assay.

Assay Cut Points

- False positive samples are eliminated in the confirmatory assay.
- The confirmatory assay false positive rate recommended by FDA is 1%

Assay Cut Points

- The cut point should be statistically determined using treatment naïve ADA negative samples.
- The cut point is initially established during assay validation:
  - Frequently using serum from healthy donors
  - Or purchased serum samples from disease population

Assay Cut Points

- Assay background signal may be different for different populations and for samples handled differently.
- The suitability of an assay cut point determined during the validation exercise should be confirmed in-study:
  - Using samples from the target population
  - Using samples handled in the same way as the clinical samples

Assay Cut Point

- 2009 guidance recommends for normally distributed data
  - Mean+1.65SD (non-log transformed data)
  - Mean*(1.65SD) (log transformed data)
- This results in a 5% false positive rate
- Using this calculation the false positive rate can range from ~2% - 11%

Shen, M., X. Dong, et al. (2015). "Statistical evaluation of several methods for cut-point determination of immunogenicity screening assay."
J Biopharm Stat 25(2): 269-279.

*EP2006 Immunogenicity and Similarity:

- One multi-dose parallel arm study in 214 patients with cancer.
- ~1583 samples obtained over time from 214 patients were tested in the applicant's ADA screening assay
- None of the samples screened positive.
- Because no sample screened positive, we deduced that the applicant did not adequately set the assay cutpoint to account for a 5% false positive rate.

*From January 7, 2015 Zarxio Ocologic Drugs Advisory Committee FDA briefing book

EP2006 Immunogenicity and Similarity:

- The applicant reevaluated the study results and established a new cut-point.
- Using the new cut-point an acceptable number of subjects screened positive.
- Final results, no patients developed ADA during the study

*From January 7, 2015 Zarxio Ocologic Drugs Advisory Committee FDA briefing book

Summary

- *Under section 351(k) of the PHS Act must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from "a clinical study or studies (**including the assessment of immunogenicity** and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and 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."

*Section 351(k)(2)(A)(i)(I) of the PHS Act. As discussed in the Background section, the statute provides that FDA may determine, in FDA's discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Summary

- At least one clinical study that includes a **comparison of the immunogenicity** of the proposed product to that of the reference product will be expected
- The goal of the clinical immunogenicity assessment is to evaluate potential differences between the proposed product and the reference product in the incidence and severity of human immune responses

Summary

- The nature and scope will depend on the nature and extent of residual uncertainty about biosimilarity after conducting structural and functional characterization and, where relevant, animal studies
- The results from immunogenicity studies support a demonstration of no clinically meaningful differences in immune response between EP2006 and US-licensed Neupogen