Biosimilar Biological Products

2013 Clinical Investigator Course

Sue Lim, M.D.
Senior Staff Fellow
OND Therapeutic Biologics and Biosimilars Team/CDER/FDA
November 13, 2013

Overview of Presentation

- Biological products
- Biosimilar biological products
  - Definitions
  - Development concepts
- Study design considerations in biosimilar development
  - Comparative clinical study (“Phase 3” trial)
- Safety
  - Biological products, biosimilars
- Questions

Biological Products

Definition of Biological Product

(Section 351, Public Health Service Act)

- The term "biological product" means a **virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein** (except any chemically synthesized polypeptide), **or analogous product, or arsphenamine or derivative of arsphenamine** (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings

What is a biological product?

- Biological products could be made of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues
- Produced in/obtained from a living system such as a microorganism, plant or animal cells, or produced by recombinant DNA technology
- Many types
  - Proteins, blood products, allergenics, vaccines, tissues, gene and cellular therapies
- Biological products make up a growing portion of new drugs approved each year[1]

[1] Nature Biotechnology 27, 11-12 (2009) doi:10.1038/nbt0109-11

Drugs vs. Biological Products - Generally

Small Molecule Drugs	Biological Products
Generally low molecular weight	Generally high molecular weight
Usually made by organic or chemical synthesis	Made with/from live cells/organisms → *inherent & contamination risk*
Fewer critical process steps	Many critical process steps
Well-characterized	Less easily characterized
Known structure	Structure may or may not be completely defined or known
Homogeneous drug substance	Heterogeneous mixtures → *May include variants*
Usually not immunogenic	Often immunogenic

Biosimilar Biological Products

Biosimilars: Regulatory Background

- Biologics Price Competition and Innovation Act (2009)
  - Created an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product
- This licensure pathway under section 351(k) of the PHS Act permits a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data
- Challenges with an abbreviated pathway for biological products include technical complexities of larger and typically more complex products, as well as the processes by which such products are manufactured

Definition: 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.

Definition: Reference Product

- the **single biological product, licensed under section 351(a) of the PHS Act,** against which a biological product is evaluated in an application submitted under section 351(k) of the PHS Act.

Note: A biological product in a 351(k) application may not be evaluated against more than 1 reference product.

Biosimilar Development: Goal

- The goal is to demonstrate biosimilarity between the proposed product and a reference product.

- The goal is not to independently establish safety and effectiveness of the proposed product.

Development Concepts

- Stepwise approach to generate data in support of a demonstration of biosimilarity
  1. Evaluate **residual uncertainty** about biosimilarity at each step
  2. Identify next steps to address the uncertainty
- Use **totality-of-the-evidence** approach to evaluate the evidence generated

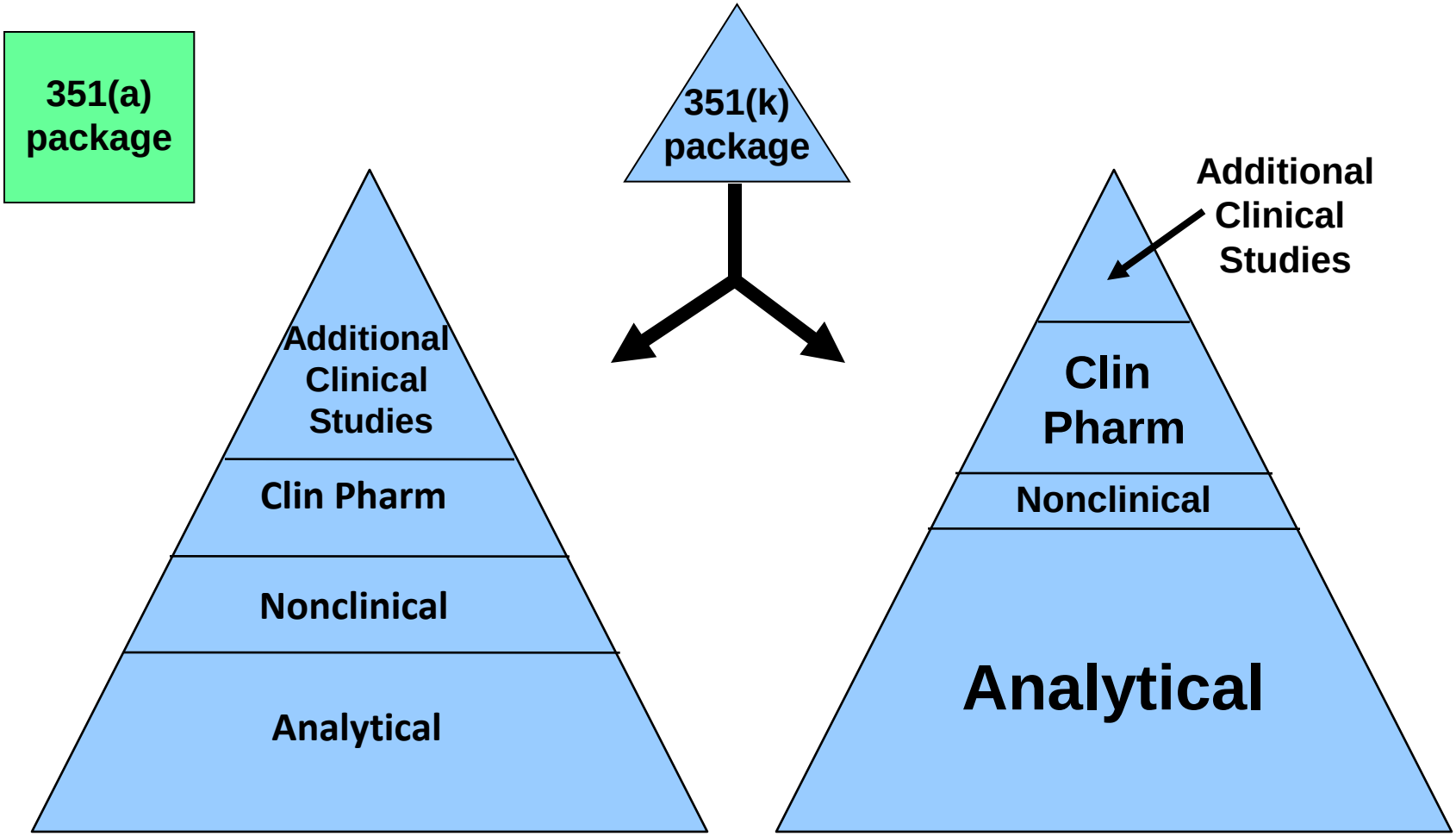
Stepwise Evidence Development

- Extensive structural and functional characterization
  - Foundation of a biosimilar development program
  - Differences can have potential effects on safety, purity and potency, and must be addressed
- Animal studies
- Human PK and/or PD studies; clinical immunogenicity assessment
- Clinical studies
  - Address **residual uncertainties** about whether there are clinically meaningful differences between products

Residual Uncertainty About Biosimilarity

- Complexity of larger proteins
  - Unlikely to be shown to be structurally identical
- Manufacturing process considerations
  - Different manufacturing processes and changes to processes may alter a protein product
- Some amount of clinical data may be needed to address residual uncertainty

Totality-of-the-Evidence



Totality of the evidence to demonstrate biosimilarity

Study Design Considerations in Biosimilar Development

(Comparative clinical study)

Biosimilars: Study Design Considerations

	Reference Product	Biosimilar
Comparator	Placebo or active comparator	Active comparator study – reference product ("no clinically meaningful differences")
Statistical study design	Superiority or non-inferiority	Generally equivalence; non-superior **and** non-inferior
Endpoint	"Outcome by which the effectiveness of treatment in a clinical trial is evaluated" [2]	Traditional efficacy endpoints may not be sensitive to detect differences between similar, active products Endpoints should reflect **activity** of the product
Time point for assessing endpoint	Adequate time for product to take and maintain clinical effect	Time point(s) when most likely to detect differences between products, e.g., ascending portion of the dose-response curve, ("activity") rather than at the therapeutic plateau ("efficacy"); look for similarity between "activity" responses

[2] Follman DA. 2007 Wiley Encyclopedia of Clinical Trials. 1-8

Biosimilars: Study Design Considerations

	Reference Product	Biosimilar
Patient population	Disease population for which licensure is sought	Same or different from the reference product Should be sensitive to detect differences; for example populations in early or late stage disease which may not be confounded by concurrent or previous therapy
Dose	Objective is to obtain clinical efficacy as efficiently and safely as possible	May be therapeutic dose, or a lower dose (if ethical) Dose should produce an effect over a time period that is conducive to detecting differences between products, e.g., therapeutic dose may reach plateau before one can assay for differences between products; lower dose may have a less steep dose-response curve
Sample size	Powered to demonstrate efficacy by detecting treatment difference	Based on the selected endpoint and margins (generally equivalence) under the chosen study conditions
Duration	Adequate to assess efficacy and reasonable safety follow-up	Driven by study design (e.g., endpoint and time point); Generally same or shorter duration because not independently establishing safety and efficacy of the product

Safety

Biological Products
Biosimilars

Biological Products and Safety

- Large complex molecules
  - More difficult to characterize to the same extent than small molecules
- Complex manufacturing process
  - Multiple steps where the product quality attributes and characteristics of the end product can be affected [3] - may impact safety and/or efficacy
  - For products extracted from human blood or plasma, risk of contamination with pathogens
- Many therapeutic protein products administered through intravenous route of administration with specific site of action
  - Immediate impact (e.g., hypersensitivity)
  - Possible no immediate reversal of effect

[3] JAMA 2008 , Vol 300, No 16

Immunogenicity

- Concern for biological products
- Impact can range from no clinical relevance to loss of efficacy and/or autoimmunity to endogenous molecules (antibody neutralization of a natural protein with biological activity)
- Immunogenicity in animals generally does not predict potential immunogenic responses in humans
  - Many biologics have specificity for human receptors and targets
  - TeGenero's TGN1412 (new compound with complex and novel MOA - CD28 agonist monoclonal antibody) – cytokine storm in HVs participating in Phase 1 study was not seen in animals [4]

[4] Lancet 2006; Vol 368; 1387-91

Immunogenicity: Biosimilars

General immunogenicity issues with biologics, plus product-specific considerations

- Immunogenicity related to clinically inactive components
  - Proposed biosimilar may have different excipients, impurities and formulation than the reference product; permissible as long as proposed biosimilar meets definition of biosimilarity
- Goal is to evaluate potential differences between the proposed biosimilar and reference product in the incidence and severity of human immune response
- Differences in immune response between a reference product and proposed biosimilar could represent a clinically meaningful difference and therefore preclude licensure as a biosimilar

Immunogenicity: Study Design Considerations

- Design can be informed by what is publicly known about the reference product
- Looking for acute hypersensitivity reactions with use of the proposed biosimilar, and comparative immune responses between products
- Factors influencing design
  - Nature of immune response (what is the response, and when does it occur)
  - Clinical relevance (extent of assessment)
  - Incidence of immune response (timing of assessment, i.e., pre- or post-market)

Immunogenicity: Study Design Considerations

- Study population
  - Consider baseline immune status; whether patients could mount an adequate immune response to detect a difference between products
  - If multiple populations available, consider the one where baseline immune status is less compromised

- Prospectively define the clinical immune response criteria
  - Some knowledge about immune profile because of publicly available information from use of the reference product

Immunogenicity: Study Design Considerations

- Immunogenicity endpoints
  - Consider immunogenicity issues that have been identified from use of the reference product
- Duration of follow-up
  - Consider time course for development of neutralizing antibodies, cell-mediated immune responses and when the expected clinical sequelae would be observed
  - Depends on length of administration of product; how the product is used (chronic dosing; intermittent; as needed)

Thank you