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Why aren't Biosimilars Generics – Regulatory Challenges

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Overview

- Background: Economic Considerations
- ANDA Submission Package
- The Path for a Small-Molecule Generics- ANDA
- Biosimilars – Guidance and Definition
- Biosimilars Development
  Emphasis
  - General Principles
- Conclusion

Background: Economics of a Crowded Generics Market

For Any $ 1 B Oral Brand			
	2 Gx	**4 Gx**	**10 Gx**
Available Market	$ 850 MM	$ 850 MM	$ 850 MM
Gx Price %	42%	20%	2%
Gx Mkt Opportunity	$ 357 MM	$ 170 MM	$ 17 MM
Gx Share	50%	25%	10%
Gx Value	$ 179 MM	$ 43 MM	$ 2 MM

As the number of competitors increase, the value for each generic is reduced dramatically

Background: Key Market Characteristics of Biologics

- Biologics sales are expected to be ~$ 170 bn by 2017
- Majority of current sales from mega blockbusters
- Monoclonal antibodies (mAbs) are the largest and fastest growing segment
- ~30% of industry pipeline in biologics
- By 2017, ~$ 70 bn in originator (reference) biologics sales are expected to lose patent exclusivity

In 2012, 7 of the Top 10 Best-Selling Pharmaceuticals Worldwide were Biologics[1]

	Product	Type	2012 Estimate[1] (USD bn)
1.	HUMIRA®	Biologic	9.1
2.	SERETIDE/ADVAIR®	Respiratory / device	8.1
3.	Enbrel®	Biologic	7.9
4.	Rituxan®	Biologic	7.0
5.	Remicade®	Biologic	6.7
6.	CRESTOR®	Small molecule	6.2
7.	Herceptin®	Biologic	6.2
8.	LANTUS®	Biologic	6.1
9.	AVASTIN®	Biologic	6.0
10.	Gleevec®	Small molecule	4.7

1 Source: Evaluate Pharma Oct 30 2012; vaccines excluded

ANDA Submission Package

- CMC
  - Demonstrate that the API is the same through the commonly used analytical approaches (IR, NMR, melting point, MS, LC-MS, impurity profile limits, etc)
  - Often rely on a 3rd party DMF
  - Use same inactive ingredients and levels (reverse engineering)
  - Use same application route and formulation type
  - Demonstrate *in vitro* equivalent release profile
  - Demonstrate adequate stability
- Clinical Studies
  - Oral: Demonstrate *in vivo* bioequivalency
  - Topical: Carry out a limited clinical study
  - Injectables: Not required in most cases
- Safety Studies
  - Mostly not required. Refer to reference product

The Path for a Small-Molecule Generics-ANDA is ..

- A well understood development and marketing path by both, the Generics industry and the FDA
- The Generics industry is well equipped (manpower, facilities, technology) to develop new generics in a relatively short period of time
- Development of a new generic product is relatively at a low cost and with a high rate of success
- A generic product is interchangeable with an FDA-licensed small-molecule reference product

Biosimilars

US Guidance *1*

- Biologics Price Competition and Innovation Act of 2009 (BPCI Act)

US Guidance 2

- 351(k) application

  licensure of an application for a biosimilar or interchangeable product under 351(k) of the PHS Act may not be made effective by FDA until the date that is **12 years** after the date on which the reference product referred to in the 351(k) application was first licensed under section 351(a) of the PHS Act. In addition, a 351(k) application may not be submitted to FDA for review **until 4 years** after the date of first licensure of the reference product

US Guidance 3

- BPD : biosimilar biological product development programs

- The BPCI Act was enacted as part of the Patient Protection and Affordable Care Act (Affordable Care Act) (Public Law 111–148) on March 23, 2010. The BPCI Act amends the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product (see sections 7001 through 7003 of the Affordable Care Act). **Section 351(k) added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product**

US Guidance *4*

- As provided by section 351(m) of the PHS Act, an additional **6-month** period of exclusivity (in which a biosimilar or interchangeable biological product cannot be licensed or accepted for review) will attach to the 12- and 4-year periods, respectively, if the sponsor conducts pediatric studies that meet the requirements for pediatric exclusivity pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Definition of Biosimilar/Biosimilarity in BPCI Act

Biosimilar* or *biosimilarity is defined in Section 351 of the PHS Act to mean that "the biological product is **highly** similar to the reference product notwithstanding minor differences in clinically inactive components, and that "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"

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

“Biosimilar” vs “NOT Biosimilar”

What are biosimilars?

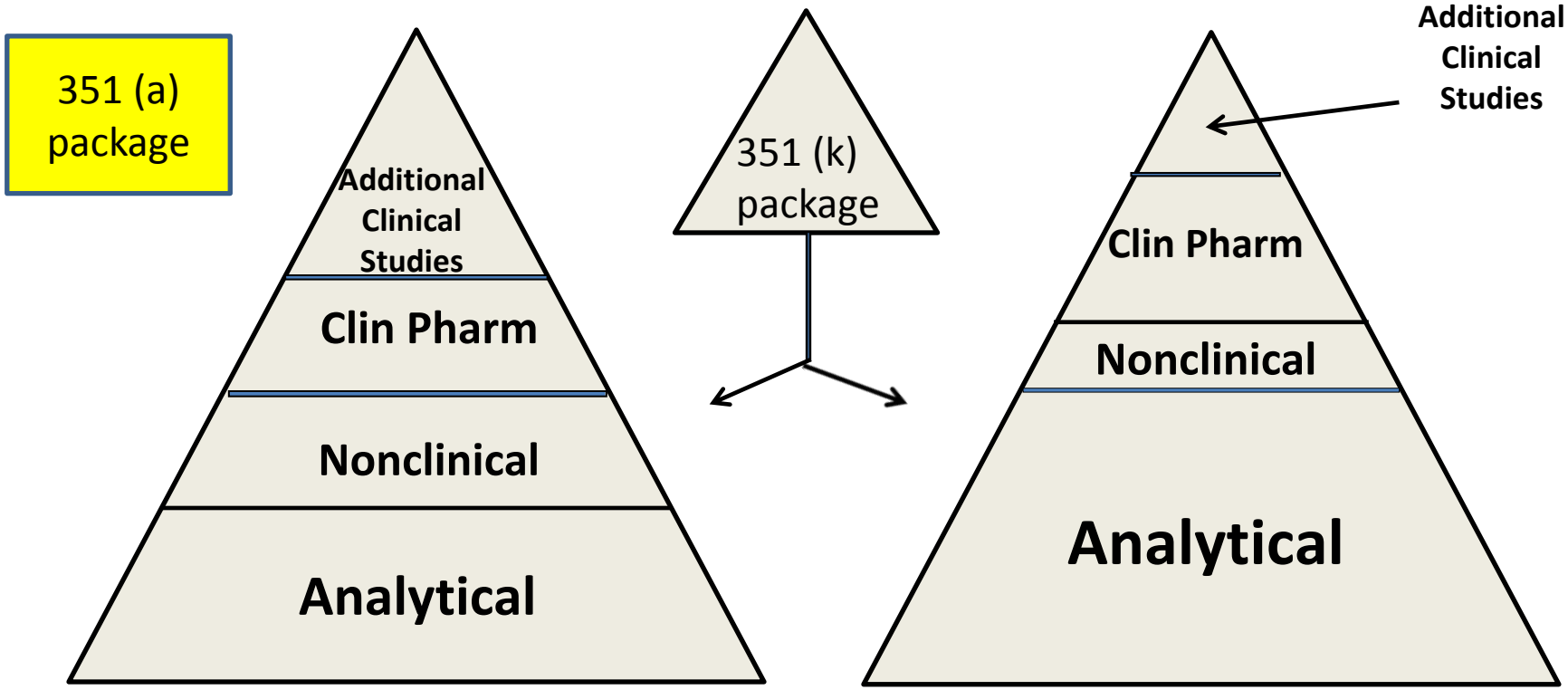
- **Biosimilars are successors to a biologic medicine which are approved via a stringent regulatory pathway**
- **Biosimilars have comparable qualit, safety, and efficacy (via clinical trials)**

What are NOT biosimilars?

- **Non-comparable 'copy biologics‘ not approved in highly regulated markets are NOT biosimilars**

Biosimilars Development Emphasis

Highly Similar Analytical and PK/PD = Lower Risk of Clinical Differences



Two approaches to achieve biosimilarity

Copied from 2012 presentation of M. Shapiro, FDA

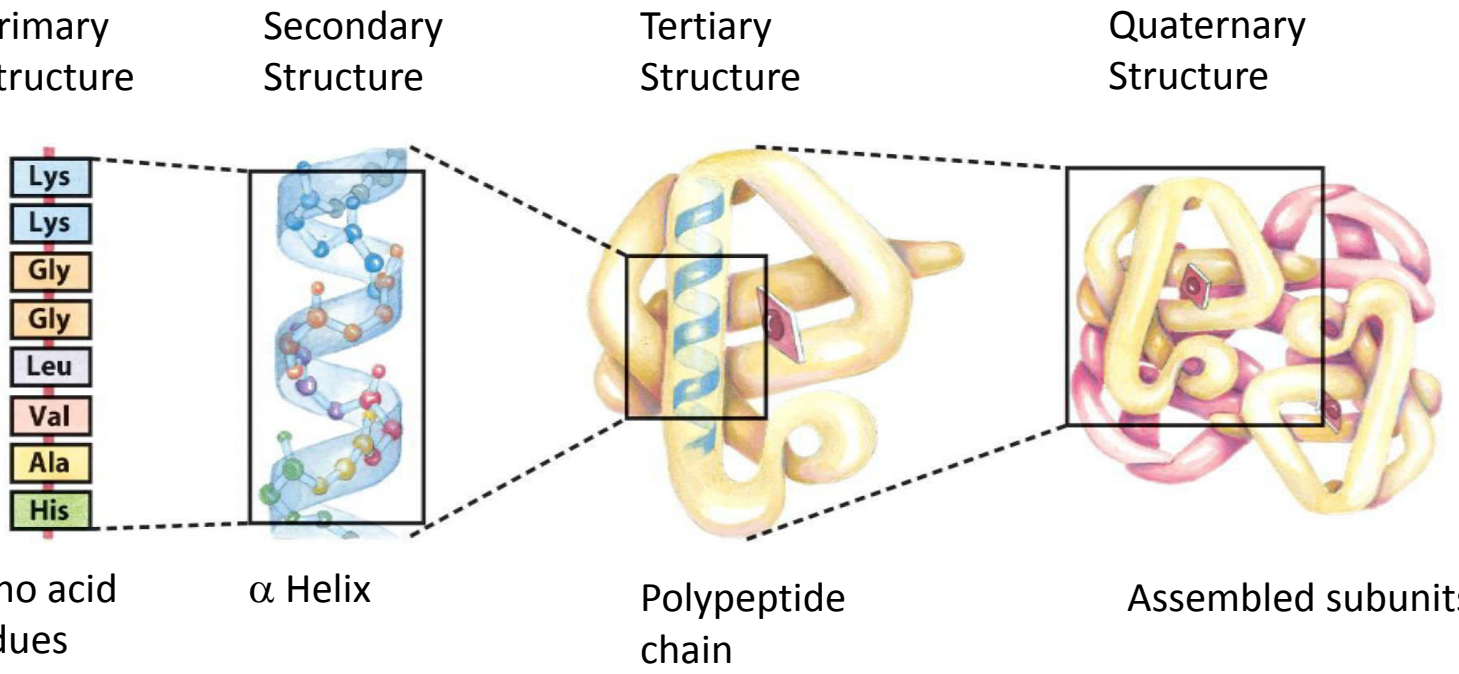
Development Approaches of Biosimilars

- A stepwise approach to demonstrating biosimilarity, which can include a comparison of the proposed 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

- The *totality-of-the-evidence* approach that FDA will use to review applications for biosimilar products

- General scientific principles in conducting comparative structural and functional analysis, animal testing, human PK and PD studies, clinical immunogenicity assessment, and clinical safety and effectiveness studies (including clinical study design issues)

The Complexity of Protein Structure

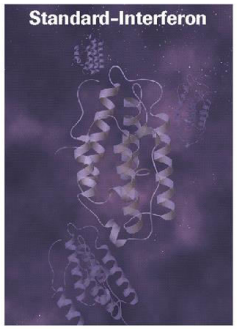


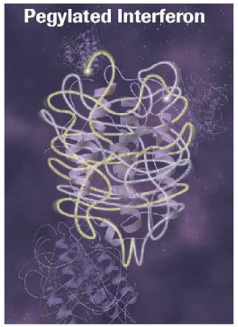
All need to be evaluated as part of analytical similarity studies

Protein Heterogeneity

- Amino Acid Substitution
- N-and C-terminal mods
- Mismatched S-S bonds
- Folding
- Truncation
- Aggregation
- Multimer Dissociation
- Denaturation
- Acetylation
- Fatty acylation
- Deamidation
- Oxidation

- Carbamylation
- Carboxylation
- Formylation
- γ-Carboxyglutamylation
- O-linked Glycosylation
- N-linked Glycosylation
- Methylation
- Phosphorylation
- Sulphation
- PEGylation





General Quality Principles:

- Importance of extensive analytical, physicochemical and biological characterization
- Product/process impurities, expression system
- Identification of lots used in the various analyses for biosimilarity determination
- Advances in manufacturing science and Quality-by-Design approaches may facilitate "fingerprint"-like analysis

Analytical Tools to Evaluate Proteins

- Amino acid sequence and modifications:
  - MS, peptide mapping, chromatographic separations
- Folding:
  - S-S bonding, calorimetry, HDX and ion mobility MS, NMR, dyes, circular dichroism, Fourier transform spectroscopy, Fluorescence
- Subunit interactions:
  - Chromatography, ion mobility MS
- Heterogeneity of size, aggregates, charge, hydrophobicity:
  - Chromatography resins; gel & capillary electrophoresis, light scatter, IM-MS, Analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, light scatter, microscopy
- Glycosylation
  - Anion exchange, enzymatic digestion, peptide mapping, CE, MS
- Bioactivity
  - Cellular and animal bioassays; ligand & receptor binding (ELISA, surface plasmon resonance), signal transduction
- Impurities
  - Proteomics, immunoassays, metal & solvents analysis