Biosimilars
The Evolving Pathway to Licensure

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Biologics Price Competition and Innovation Act

- Healthcare Reform – Title VII
  - Signed into law March 23
- Public Health Service Act Amended
  - New 42 U.S.C. 262(k)
  - Licensure of “Biosimilar” and “Interchangeable” Biological Products

Two Standards for Licensure

- Biosimilarity
  - "Highly similar" to reference product
    - "Notwithstanding minor differences in clinically inactive components"
  - "No clinically meaningful differences" re safety, purity and potency
- Interchangeability
  - "Can be expected to produce the same clinical result" in "any given patient"
  - Risk of safety or diminished efficacy of alternating or switching not greater than the risk of continued use of reference product

Biosimilar Application

- Studies re characterization, safety, and efficacy
  - Analytical studies to show “highly similar”
  - Animal studies
    - Including assessment of toxicity
  - Clinical study or studies
    - including immunogenicity stud(ies)
    - For one or more appropriate conditions of Reference Product
- FDA can waive any of these study requirements

Biosimilar Application

- Pediatric Studies required for approval of NDAs
  - Biosimilar considered to be new active ingredient
    - Unless FDA determines Biosimilar to be “interchangeable”
- Other Information
  - Same mechanism(s) of action
    - To extent known for Reference Product
  - Conditions licensed for Reference Product
  - Same strength, dosage form, and route of administration
  - Manufacturing facility/processes
  - REMS if requested by FDA
  - Optional information -- Interchangeability

More Restrictive than Hatch-Waxman Scheme

- No pathway analogous to 505(b)(2)
  - No new condition of use
  - No new active ingredient
  - No difference in strength, dosage form, route of administration
  - No reliance on more than one Reference Product
  - No clinically meaningful differences in safety or efficacy

Exclusivity for Reference Product

- Exclusivity for original BLA licensure
  - 12-year delay in licensure of Biosimilar
  - 4-year delay in submission of Biosimilar application
  - Delay calculated from date of original licensure of Reference Product
- No new exclusivity for product changes made through license supplements
- Pediatric and orphan exclusivity

Exclusivity for Modification

- Limited exclusivity for new BLA for modification to previously licensed biologic
  - Same sponsor or
  - Same manufacturer
- Exclusivity only for:
  - Modification to "structure" that affects safety, purity, or potency
  - "Non-structural" change that does not result in new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength
    - Possible exclusivity for OTC switch, different safety or efficacy profile, new sponsor and manufacturer

Exclusivity for Interchangeability

- For first biosimilar determined interchangeable
- Delays determination of interchangeability for subsequent biosimilars
- Periods of delay -- earlier of:
  - One year after the first commercial marketing
  - 18 months after final court decision or dismissal re all patents subject to infringement suit under patent resolution provisions
  - 42 two months after determination of interchangeability -- if lawsuit still pending
  - 18 months after licensure -- if no lawsuit filed

Transitional Provisions for Protein Products

- Proteins and analogous products added to definition of “biological product”
  - Exception for chemically processed polypeptides
- Some classes of proteins historically approved as drugs rather than licensed as biologics
  - Hormones
  - Insulin

Transitional Provisions for Proteins (cont.)

- During 10-year period following enactment:
  - NDA or ANDA can be filed for product within class of proteins for which an NDA was approved prior to enactment of biosimilar provisions
  - Unless there is a BLA for an appropriate reference drug
- 10 years after enactment date:
  - Proteins approved as drugs deemed to be licensed as biologics
  - No protein application can be submitted under drug approval provisions

Other Provisions

- Patent resolution outside of FDA approval process
- Processes for FDA guidance documents
  - Public input
- Process for FDA recommendation re user fees

The Current Debate

- Acceptable range of structural differences
  - Post translational modifications
- Necessity for clinical trials
- Demonstration of clinical similarity
  - Comparisons to drugs approved in foreign jurisdictions (highly similar to U.S. product)
  - Extrapolation across indications
  - Clinical superiority
- Evidence demonstrating interchangeability
- Nomenclature and labeling
- Modifications entitled to exclusivity