Follow-on Biologics/Biosimilars - US Situation

10 August 2007

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Topics

- Biologics—the science
- Biologics—the regulation
- Biologics—follow-on biologics

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Biologics - Science

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Biologics are…

- Derived from living material (plant, animal or microorganism)
- Derived from natural sources or engineered
- Usually based on a protein or nucleic acid
- Used for the treatment of diseases in humans

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How are Biologics Different from Small Molecule Drugs?

- Composition, Size, Structure
- Manufacturing
- Clinical Safety

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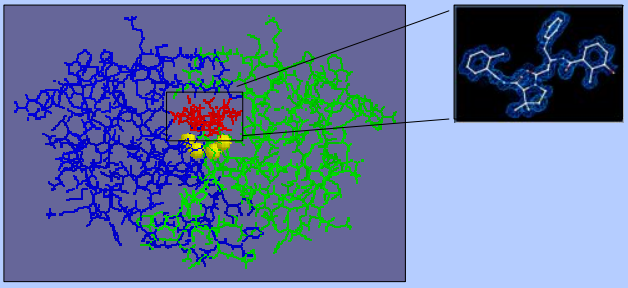
HIV-1 Protease (small protein) with inhibitor (small molecule drug)

- Protease MW 21,000
- Inhibitor MW 700



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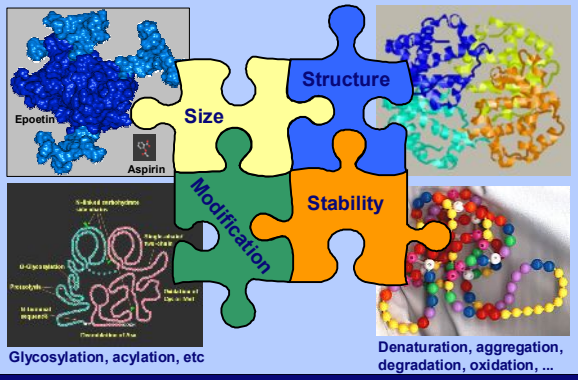
Manufacturing Process

- Chemically-based drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions
  - This is Organic Chemistry
- Biologics are made by harvesting the substances produced and secreted by constructed cells
  - This is Genetic Engineering

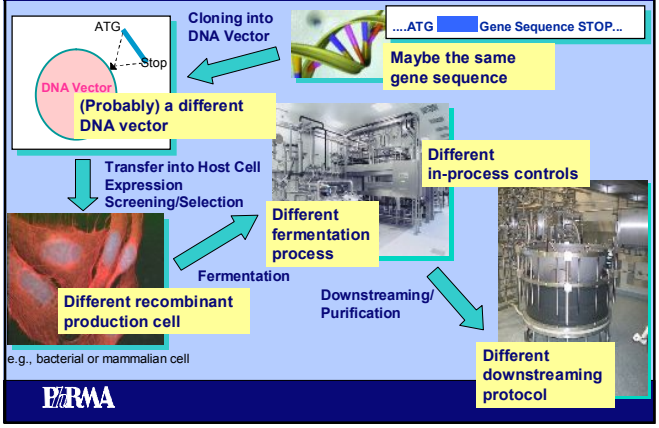
The Protein Challenge: Complexity



Glycosylation, acylation, etc

Denaturation, aggregation, degradation, oxidation, ...

Different Protein Manufacturers Use...



Clinical Safety - Immunogenicity

- Small molecule drugs rarely elicit immune response
- Macromolecules (proteins) of biologic drugs are capable of triggering immune response with varying consequences

Differences Between Small Molecule Drugs and Biologics Translate into Several Key Facts

- Biologic drugs are orders of magnitude more complex than small molecule drugs
- Safety & efficacy of final product exquisitely sensitive to small differences in process
- It is difficult to predict the effect of these small differences without clinical data
- Potential for dramatic negative health consequences with insufficient testing

US Regulatory Environment

FDA Approval Pathways

- Small molecule drugs approved through *New Drug Application (NDA)*
  - Regulatory framework set out in Food, Drug, and Cosmetic Act (1938, as amended)
  - FDCA section 505
- Biologic drugs licensed through *Biologics License Application (BLA)*
  - Regulatory framework set out in Public Health Services Act (1902, as amended)
  - PHSA section 351

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FDCA versus PHSA

- Pathways for abbreviated approvals exist under FDCA section 505
  - This is how generic drugs are approved
- Pathways for abbreviated approvals do not exist under PHSA section 351
  - No pathway for generic or follow-on biologics

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Some Biologics Are Approved under FDCA

- For historic reasons, FDA evaluates and approves some biologics under Section 505
- FDA administrative policy, not statutory
- Examples include insulin and other hormones

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Follow-on Biologics or Biosimilars

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Key Principles: Follow-on Biologics or Biosimilars

- Patient Safety—Science Based Regulation
  - Follow-on biologic will be similar to - not the same as - the innovator product
  - Follow-on biologic applicant must demonstrate safety & efficacy through clinical studies
  - Science does not support automatic substitution
- Incentives for Innovation

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Key concepts for Safe and Effective Follow-on Biologics

1. Clear regulatory pathway for new product category distinct from small-molecule generics: FOBs/biosimilars
   - Open, transparent process with category-specific guidance, including a stepwise approach for products to be covered
   - Using reference products that have extensive clinical data and market experience, approved with full data package and review
   - Includes a distinct naming and labeling system (clear prescribing, dispensing and surveillance)
2. Adequate quality standards
   - Products need to have similar molecular structural properties
   - Same quality standards as for innovative products
   - Robust comparative physico-chemical and biological characterization to be specified
3. Adequate pre-clinical and clinical testing requirements
   - Case-by-case approach within the scope of pre-defined non-clinical and clinical requirements, demonstrating safety and efficacy
   - Clinical data for each indication unless otherwise scientifically justified
   - Appropriate risk management and active pharmacovigilance
4. Appropriate use
   - Science does not support automatic interchangeability/substitution

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Follow-on Biologics and Incentives for Innovation

- Development of biologics is time-consuming, costly and risky
- Important to encourage innovation in new biological products
- Efforts from innovators need protection
  - Patents (e.g. composition of matter, methods of using products and methods of manufacturing)
  - Trade secrets
  - Data and market exclusivity

Follow-on Biologics - US Legislative Situation

- Senate
  - Hearings held Spring 2007
  - Legislation passed out of Committee June 2007
  - Key elements
    - 12 years of data exclusivity
    - Complex patent construct of concern to industry
    - Testing and interchangeability requirements raise patient safety concerns
- House of Representatives
  - Hearings held Spring 2007
  - No legislation drafted to date

Summary

- Science of biologics is extremely complex and quite different from small molecule drugs
  - A follow-on biologic will be similar to, but not identical to, the innovator biologic
- Any approval pathway for follow-on biologics must protect patient safety by
  - Ensuring safety and effectiveness through adequate clinical and pre-clinical testing
  - Ensuring product quality through a full manufacturing and analytical testing package
  - Not allowing for automatic interchangeability
- Any approval pathway must also include support for continued innovation through
  - Extended (>14 years) data exclusivity
  - Adequate patent protection