Biologics: Status, Oversight, and Commercialization
Bryan A. Liang, MD, PhD, JD, UCSD School of Medicine,
San Diego Center for Patient Safety

Biologic Drugs
• Biologics are:
  – cutting edge biotech drugs and diagnostics.
  – physiological proteins made in living cell lines from bacteria, yeast, and mammals.
  – Address fundamental processes of disease at (usually) cellular level.
• Huge impact on society.
  – >325 million persons treated using biologics.
  – Treats most serious diseases and vulnerable patients, e.g., hepatitis, cancer, AIDS.

But …
• Biologics represent a huge healthcare cost.
  – can reach >$100,000 in treatment costs annually.
  – global market growing at least twice as fast as that for small molecule drugs.
  – comprises ~15-20% of total pharmaceutical sales.
  – represents nearly 1/3 of the global development pipeline.
  – 2016: 7/10 top pharmaceuticals globally will be biologics.
• Top five Medicare Part B drugs administered in physician offices are biologics.
  • Top drug—erythropoietin—$2 billion.
  • Greater than entire budget of FDA.
So …

Advent of Biosimilars/Follow On Biologics

- Key Question: Can we make cheap copies of branded biologics, i.e., biosimilars?
- Look at science of biologics:
  - Assess complexity: Size; Manufacturing
  - Assess safety issues: Immunogenicity; Excipients
- Look at extant regulation of biosimilars approval:
  - USA Biologics Price Competition and Innovation Act
  - EU Biosimilars System
- Look at market status for biosimilars.

Complexity: Size

- Biologics (injectables) much more complex than chemical medicines (pills).
  - Molecular size:
    - E.g., aspirin: 180; erythropoietin, 30,000.
  - Chemical medicines completely characterized by molecular formula (C$_9$H$_8$O$_4$); biologics only approximated at best (1˚, 2˚, 3˚, and sometimes 4˚).

Complexity: Size Impact

- Tiny changes in protein can have devastating results, e.g., sickle cell anemia (one amino acid).
Complexity: Mfg’ing

• Much more complex manufacturing.
  – e.g., quality tests: 40-50 versus 200-300.

• “Swirling flasks” versus growing organisms.

Complexity: Mfg’ing

• Chemical medicines can be copied identically—generics.
  – Atom by atom chemical formula comparisons and bioequivalence testing.
  – Homogeneous material perfectly characterized due to small size and relatively simple structure.

Complexity: Mfg’ing

• Biologics can never be copied identically.
  – Like humans, diversity of living organisms create variation—actual biosimilar product, side products, nascent cell proteins.
  – Biologic biosimilar “product” actually heterogeneous mix imperfectly characterized by shape and gross geometry due to immensity.
**Complexity: Mfg’ing**

- Exquisite sensitivity of biologic manufacturing:
  - PK/PD characteristics change moving manufacturing from one site to another.
  - Most discovered issues were in cooperative licensing technology transfer and use for a branded product.
  - Biosimilars are NOT manufactured under cooperative licensing between competitors!

**Safety: Immunogenicity**

- Chemical drug tiny size generally does *not* induce body immune response.
- Biologics large size associated with *immunologic* reactions.
  - Some responses are good: vaccines.
  - Unwanted immunogenicity responses can be devastating/life threatening.
- Immunogenicity very hard to predict for all biologics – branded and biosimilars.

**Safety: Illustration – Eprex**

- Epogen/Eprex (erythropoietin) made by Amgen and J&J using same “recipe.”
- Amgen product in US, J&J in EU.
- 2000, hundreds of EU reports of pure red cell aplasia (0 reports in US).
  - PRCA: body stops creating red blood cells.
  - Patients die; those alive found to have allergic immunogenicity reaction to Eprex.
  - Patients found to be allergic to all erythropoietins, including body’s own.
- From first report to present, hundreds of scientists researching cause.
- Current (debated) explanation: stabilizing agent interacted with rubber stopper.
Safety: Excipients

- Biologic excipient (non-active ingredient) reactions.
  - Intravascular hemolysis.
  - False elevated glucose.
  - False negative hepatitis B results.

Extant Regulation-New Drugs

- FDCA: New Drug Application (NDA).
  - All chemical and some “simple, relatively small, well understood biologic” drugs.
- PHSA: Biological License Application (BLA).
  - Complex biologics, e.g., monoclonal antibodies, vaccines.
  - Both extensive before marketing approval given:
    - Require preclinical studies showing PK and PD info.
    - Requires clinical studies showing safety and efficacy.
    - Requires demonstration of good manufacturing practices.
- Costs:
  - NDA: ~$800 million.
  - BLA: ~$1.2 billion.

Extant Regulation-Generics

- To speed cheaper generic versions of chemical drugs to market post-patent expiry, Hatch-Waxman Act passed in 1984.
- New FDCA §505(j)—created ANDA: Abbreviated New Drug Application.
  - Generic firms can rely on originator safety and efficacy data.
  - Must only show chemical equivalence and bioequivalence.
  - Generics will be substitutable for originator drugs (“AB rated”).
  - Most chemical generics go through this process.
- Note: to balance, brand name companies get 5 years data exclusivity.
Extant Regulation-Biosimilars

- USA Biologics Price Competition and Innovation Act (BPCIA).
- Part of Healthcare Reform bill (ACA).
  - Pathway for biosimilars approval:
    - Mfg’er may submit a Biosimilar Biological Product Application (BBPA).
  - Reqs:
    - Product must be “biosimilar” to a single reference product.
    - Must share same MURDS characteristics: mechanism, use, route of administration, dosage form and strength.
    - Facility that manufactures the biosimilar must meet safety and purity standards [cGMP].

Extant Regulation-Biosimilars (cont.)

- Def: “biosimilar” product:
  - “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and
  - no “clinically meaningful differences” between the two products.
- Studies:
  - 1) analytical studies demonstrating the high degree of similarity;
  - 2) animal studies, including toxicity assessments, and
  - 3) at least one clinical study demonstrating safety, purity and potency.
- Branded biologics given 12 years data exclusivity.

Extant Regulation-Biosimilars (cont.)

- Interchangeability: a biosimilar filer may also show proposed product is “interchangeable” with reference product [no EU equivalent].
  - An interchangeable product “may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.”
  - FDA may award first interchangeable product market exclusivity.
- Interchangeability requires product:
  - 1) is biosimilar,
  - 2) is expected to produce the same clinical result as reference product, and
  - 3) a switch or alternation between products will not pose an increased risk in terms of safety or efficacy.
- Big debate on whether pharmacists must notify prescribing MD of substitution.
Extant Regulation-EU Biosimilars

- EU adopted biosimilars regulation in 2004.
  - General: clinical/nonclinical requirements and quality requirements.
  - Annex guidance: on insulin, human growth hormone, erythropoietin, G-CSF, etc..
- Allows biosimilar applicant reliance upon regulator knowledge of originator/reference molecule safety and efficacy.

Extant Regulation-EU Biosimilars

- Requires clinical trials to show:
  1. Comparability and clinical differences between biosimilar and reference drug.
  2. 12 months of immunogenicity data with specified populations.
  3. Other clinical studies if requested and relevant.
  4. Full pharmacovigilance and risk management plan.

EU 2011, 2013/2014 Draft Biosimilar Revisions

- 2011: Revisions begin for EU biosimilars regulation.
- Q4 2013: Final recommendations due after comments.
- Q2 2014: Final review and revisions.
- In general: European Medicines Agency recommends:
  - more risk-based studies to determine need for in vivo studies;
  - clearer guidance on clinical trials, and
  - clarification on addressing biosimilar v. originator immunogenicity.
Risk-Based Studies
- Draft: employ risk-based approach to non-clinical biosimilar review.
  - In vitro studies should be conducted first, and on its basis determine specific in vivo work needed.
  - Decision to proceed to in vivo studies should take account:
    - Biochemical—drugs may have in vivo effects not fully elucidated in in vitro studies.
    - Presence of quality issues not detected in the reference product such as significant differences in quality attributes between the reference drug and biosimilar, and/or relevant differences in formulation.
  - If in vivo studies are deemed necessary:
    - Animal species or other model should be considered, unless such a model is not available, in which case the product should be taken to clinical trials for pK and pD studies.

Clinical Trials
- If needed, must:
  - Show comparable clinical efficacy of the biosimilar and reference drug.
  - Be adequately powered, randomized, parallel-group comparative clinical trials, preferably double-blind.
  - Use of non-inferiority design may be acceptable if "justified."

Immunogenicity
- Biosimilar sponsors must:
  - Address possible immunogenicity potentially arising from different manufacturing process of reference drug.
  - If higher, calls the product’s biosimilarity into question.
  - If lower, "would not preclude approval as a biosimilar."
  - If there is reduced development of neutralizing antibodies with the biosimilar, the efficacy analysis of the entire study population could erroneously suggest that the biosimilar is more efficacious than the reference product. It is therefore recommended to pre-specify an additional exploratory subgroup analysis of efficacy and safety in those patients that did not mount an anti-drug antibody response during the clinical trial.
  - If the originator has more than one indication, then the biosimilar’s efficacy and safety must be "justified, or if necessary demonstrated, for each of the claimed indications."
Policy Foundational Concerns

- **Information gaps?**
  - Large gaps in science-based characterization: complex biologics and prediction of safety issues difficult.
- **Populations at risk?**
  - Socially vulnerable: needing cheapest price (uninsured/ACA gaps), medically vulnerable—cancer, AIDS patients.
- **Potential Harm?**
  - High severity: life-threatening adverse events, e.g., immunogenicity.
- Policy philosophy: “Higher and Greater”: info gaps, vulnerable patients, and potential harm means **err on side of safety.**

Who, What, and How?

- **Who**: global pharmerging market players (BRICS countries).
- **Other Markets**: frontier markets (MINT markets).
- **Companies**: Merck [bio-betters]; Merck-Serono; Boehringer Ingelheim; Samsung-Biogen-Idec; Pfizer; Amgen-Actavis; Novartis-Sandoz; Celltrion-Hospira; Teva-Cephalon; plus more every day.
  - cf. the “anti-biosimilars company”: Roche.

Who, What, and How? (cont.)

- **What**: generally mAbs (Herceptin/trastuzumab; Rituxan/rituximab; Remicade/infliximab).
  - 2012: 73 mAbs under development.
    - ~30 companies working on trastuzumab (Herceptin) alone – EU patent expiry 2014 (USA 2019).
    - 59 preclinical stage; 5 in Phase II; 3 in Phase III
  - Current record of biosimilar applications in EU.
    - 7 in 2012 cf. 0 in 2011, 0 in 2010, 1 in 2009 (total approved 2004-2012: 15).
  - 2013: First EU biosimilar mAb approved: Inflectra/Remsima by Hospira/Celltrion (infliximab); biosimilar of Remicade by J&J.
  - 2013: First Indian “similar biologics” mAbs approved: Hertrace/CemAb (biosimilar of Herceptin by Mylan/Biocon); Mabtas (biosimilar of Rituxan by Intas).
**Who, What, and How?**

- **How:** Limited commercialization success: biosimilars represent <0.5% of biotech drug spending in developed markets.
  - 2013 sales ~$1.1-1.2 billion; cumulative sales from 2006-2011 ~ $1.2 billion
    - Cf. R&D, manufacturing costs of $1-1.5 billion per biosimilar.
    - Only G-CSF/neupogen biosimilars have in total >50% penetration in any market.
    - Price discounting ~20% (cf. small molecule generics at ~90%).
- **Jump start efforts:** e.g., Norway: will fund clinical studies for biosimilar Remicade versions (Inflectra) to reassure MDs of safety and efficacy.
  - reflects high caution among MDs across countries,
  - small number of manufacturers across products, and
  - only modest price discounts.

**Future Considerations**

- **Biosimilar market:** will grow to between $2-22 Billion/annually.
- **Maturity:** small molecule generics took >10 years to be accepted.
- **Potential:** 6 largest mAbs off patent by 2019.
  - Sales: E.g., Remicade/infliximab ~ $6 billion alone; ~$60 billion total.
  - Locales: Emerging/Frontier Markets: both producers and consumers; clinical trials locales (e.g., Colombia and South Korea marketing and mfg’ing approval for infliximab biosimilar/Inflectra by Celltrion; Brazil proposing ‘similar biologics’ be treated as generics).
  - Demand: E.g., Brazil: mAb treatment use 1/3 of UK, 1/6 of USA; large potential channel.
- **“Success” of biosimilars:** dependent upon large generics, small generics, branded companies, and payors to coordinate efforts.
  - Key: agreement on exclusivity, markets, promotion, and regulatory oversight.

**Overall**

- **Biologics have provided incredible social benefits.**
- **Costs are high; biosimilars may address.**
- **Biosimilar situation like generic chemical drug era.**
- **Global biosimilars have significant risks and upside benefits.**
- **Success will be dependent upon technical, finance, and payor characteristics** in each particular market.