

Landscape for “Generic Biologics” in the U.S.

SABPA

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Generic Drugs in the United States

- Since 1984, over 10,000 generic drugs entered the U.S. market.
- In 2005, generic drugs accounted for close to 50 percent of prescriptions filled in U.S..
- Six of seven important generic drugs are priced lower in U.S. pharmacies than in Canadian pharmacies.

Source:

FDA Office of Generic Drugs web page accessed Oct 30, 2006.

Regulatory Basis for Generic Drugs

- Hatch-Waxman Amendments to the Food, Drug and Cosmetic Act (1984)
 - Created an abbreviated application process for generic drugs that were shown to be equivalent to an approved drug.
 - Included certain recombinant proteins
- Biologics, which are regulated under the Public Health Service Act, were not affected by Hatch-Waxman.

Regulatory Basis for Generic Drugs

- Hatch-Waxman 1984 Amendments to the Food, Drug and Cosmetic Act:

Drug Price Competition and Patent Term Restoration Act

Innovator drug manufacturers have incentives for R&D

- Patent protection and extension to offset regulatory review time
- Marketing exclusivity enables innovators to recoup investments.

Upon expiration of patent protection and marketing exclusivity for new drugs, consumers benefit from rapid availability of lower priced generic versions of innovator drugs.

Pressures to Enable Lower Cost “Generic” Biological Products

In 2005, the five largest Medicare Part B drug expenditures were all for biotech drugs.

- Epogen, \$1,750,000,000
- Aranesp \$ 850,000,000
- Procrit \$ 776,000,000
- Remicade \$ 541,000,000
- Neulasta \$ 524,000,000

Source: CQ Weekly, Oct 2, 2006, citing CMMS 2005

Drug Approval Mechanisms under Hatch-Waxman 1984

- Food, Drug and Cosmetic Act Section
 - 505(b)(1)
 - Applicant submits NDA containing full safety and effectiveness studies
 - Product wins approval on the merits of its own data

Drug Approval Mechanisms under Hatch-Waxman 1984

- Food, Drug and Cosmetic Act Section
 - 505(j)
 - Used for a product that is identical to an innovator product in drug substance, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use.

Drug Approval Mechanisms under Hatch-Waxman 1984

- Food, Drug and Cosmetic Act Section
 - 505(b)(2)
 - New Drug Application which
 - relies on investigations which "were not conducted by or for the applicant" and for which the applicant has not obtained a right of reference, or
 - relies on specific published data that is necessary to support approval
 - The applicant must show the product is equivalent to an approved reference (innovator) drug in which FDA has found evidence of safety and effectiveness.

Omnitrope rhuGH

- Recombinant human Growth Hormone
- Non-glycosylated, very well-characterized protein, regulated under FDCA.
- Seven prior GH products approved by FDA as 505(b)(1) NDAs
- Sandoz submitted 505(b)(2) NDA submitted for Omnitrope in 2003
 - NDA included human original clinical safety and efficacy data
 - NDA included full CMC, PK, Tox data
 - NDA included comparative physicochemical and biochemical data showing equivalence of the GH molecule to already approved Genotropin
 - Claimed 505(b)(2) NDA

Omnitrope rhuGH

- Pfizer objected, citing no legal basis to refer to trade secret Genotropin (somatropin) data.
- Other industry members objected, citing no basis to approve a biologic under 505(b)(2).
- FDA delayed approval, citing unclear legal issues
- Sandoz sued FDA and Federal Judge ordered FDA to make a final decision on Omnitrope NDA
- In May 2006 Omnitrope rhuGH was approved via 505(b)(2) NDA pathway.

Follow-on Biologic in U.S.

- Is Omnitrope a generic biologic?
- No.
 - FDA says that Omnitrope is not a generic biologic as no therapeutic equivalence was established.
 - Omnitrope is more appropriately called a follow-on biologic, per FDA

FDA Draft 505(b)(2) NDA Guidance

- Defines what the 505(b)(2) application must include:
- Identify all listed drugs for which the 505(b)(2) seeks to rely on the Agency's previous finding of safety or efficacy. Identify application components relying on FDA's finding of safety and effectiveness of a previously approved drug product.
- Conflicting Patent information and Patent certifications required by FDC Act.
- Information required if the applicant believes it is entitled to marketing exclusivity.
- Bioavailability/Bioequivalence (BA/BE) data comparing the proposed product to the listed drug (if any).
- Bridging studies or other studies necessary to support the change or modification from the listed drug or drugs (if any).
- FDA will provide guidance on a case by case basis.

Possible Future Follow-on Biologics Potentially Eligible under 505(b)(2)

- All recombinant insulins
- Calcitonins
- Follistim (follitropin beta)
- Natrecor (nesiritide)
- GnRH agonists/antagonists
- Iplex and Increlex (IGF-1)
- Somavert (pegvisomant)
- Symlin (pramlintide)
- Thyrogen (thyrotropin)

Considerations with Biologics and Conventional Drugs

Biologics

- Regulated under PHS Act
- Protein- or carbohydrate-based product
- Extracted from living entity
- Complex physicochemical structure
- Less well-defined
 - Macromolecule
 - Tertiary structure
 - Glycosylation
- Manufacturing process defines product
- Potential immunogenicity
- Heat and shear sensitive

Conventional Drugs

- Regulated under FDC Act
- Synthetic organic compounds
- Defined structure, physical & chemical characteristics
 - Chemical synthesis
 - Small molecule
- Unlikely immunogenicity
- Stable

Landscape in U.S.

- Political pressure mounting to enact legislation to approve lower cost comparable biologics
 - 5 largest Medicare Part B drug expenditures are all for biologics.
 - Currently under PHS Act, FDA can not recognize a generic biologic without new legislation.
 - Opponents to biogenerics argue that biologics require specialized manufacturing and analytical tools to ensure quality and predictable safety, potency, purity, and efficacy.
 - Advocates of biogenerics argue that
 - best practice technology is capable of demonstrating that certain generic biologics are comparable to innovator products
 - One can expect comparable safety and efficacy in such cases to justify FDA approval if enabling legislation were in place.

Do generic biologics exist elsewhere?

- EMEA adopted Biosimilar legislation in 2004
- Directive and guidance documents establish parameters for approval but provide for case-by-case review of each biosimilar candidate
- Guidelines for biosimilars are drafted or published for recombinant proteins such as
 - rHu-Erythropoietin
 - rHu-Granulocyte Colony Stimulating Factor
 - rHu-Somatropin
 - rHu-Insulin
 - Other recombinant proteins

Sep. 29, 2006:

Proposed “Comparable” Biologics Legislation

- H.R. 6257 and S.B. 4016
- Would amend the Public Health Service Act to authorize the Secretary of HHS to approve abbreviated applications for biological products that are “comparable” to previously approved (brand name) biological products.

Key Provisions of the Comparable Biologics Proposed Legislation

- Creates a comparable biological product defined
 - the absence of clinically meaningful differences between the comparable biological product and reference product in safety, purity, and potency....
- Defines a comparability determination
 - based on “data derived from chemical, physical, and biological assays...and...any necessary clinical study(ies) sufficient to confirm safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used.”

Key Provisions of the Comparable Biologics Proposed Legislation (2)

- Defines a requirement for comparable principal molecular structural features of the reference and comparable biological product based on ... testing appropriate ... to identify differences ... relevant to safety, purity or potency."

Key Provisions of the Comparable Biologics Proposed Legislation (3)

- Defines comparable principal molecular features to include products that:
 1. “**differ in** structure due solely to post-translational events, infidelity of translation or transcription, or minor differences in amino acid sequence;”
 2. have “similar saccharide repeating units, even if the number of units differ and even if there are differences in post-polymerization modifications;”
 3. are glycosylated and have characteristics of #1 and/or #2 above
 4. have identical polynucleotide sequence;
 5. are “closely related, complex partly definable biological products with similar therapeutic intent, such as two live viral products for the same indication.”

Key Provisions of the Comparable Biologics Proposed Legislation (4)

- Requires data “demonstrating that the comparable biological product and reference product utilize the same mechanism of action....”
- Requires applicants of the comparable product to propose in labeling the same, previously approved “conditions of use prescribed, recommended, or suggested....”
- Requires the comparable product to use the same route, and have the same dosage form, and strength as the reference product.

Key Provisions of the Comparable Biologics Proposed Legislation (5)

- Manufacturing facility must meet standards designed to ensure that the product continues to be safe, pure and potent.
- Requires applicants that don't have access to innovator's data to submit their own data to demonstrate that the comparable product application "contains sufficient information to establish the safety, purity, and potency of the biological product relative to the reference...."
- Gives the comparable product applicant the option to perform post-marketing study(ies) similar to those required of the reference product but no others.

Key Provisions of the Comparable Biologics Proposed Legislation (6)

- Sets a final action date for FDA review
 - of an abbreviated comparable biological product application
 - at eight (8) calendar months following Sponsor's submission of the application or
 - 180 days after FDA notifies the Sponsor that its application has been accepted for filing, whichever is earlier.
- Allows comparable product manufacturers to state that their product is interchangeable with the reference biological product.

Potential Concerns with H.R. 6257 and S.B. 4016

- Lack of an efficacy demonstration requirement in the absence of a bioequivalence determination.
- Possible obstructing regulators from determining incomparability when certain key molecular differences exist.
- Allows applicants to bypass certain comparability determinations if they lack access to data from a reference product.

Healthy Useful Debate

Deliberation in Congress to pass legislation that would enable FDA to approve a "comparable biologic" under the PHS Act will be closely watched in the next Congress.

Conclusion

- Movement toward additional approval of 505(b)(2) Follow-on biological products is inevitable following the high profile approval of Omnitrope.
- Enactment of legislation to create a “biosimilar” approval mechanism in U.S., under the PHS Act, grows more likely as biologics increase their share of FDA approved products each year.