Biosimilars:
Unpacking Complex Issues

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Biomedical science is increasingly moving towards the development of biologics: complex pharmaceuticals derived from living organisms and tissues that can provide targeted treatment for diseases.[8] They have much higher rates of success, especially for the treatment of autoimmune diseases and cancer, compared to so-called small-molecule pharmaceuticals, which are synthesized through a chemical process and make up the bulk of medications currently prescribed in the U.S.[9] Due to their complexity, biologic drugs cost much more to develop than their small-molecule counterparts, and have been criticized because of their high prices.[10] Some analysts argue that the approval of biosimilars – drugs that have the same mechanism of action as the original, or reference, biologics – will help to contain costs after reference biologic patents expire.[11]

Between 2013 and 2015, approximately $20 billion worth of biologic products were expected to lose their patents, creating an opening for biosimilars to enter the market.[12] However, until recently, the United States has not had a regulatory pathway for the approval of biosimilar drugs.

Unlike generic versions of more traditional small molecule drugs, which are regulated by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), biosimilars are not identical to their reference biologics and face different regulations. A provision in the Affordable Care Act (ACA), the Biologics Price Competition and Innovation Act (BPCIA), allows for the creation of biosimilars that have the same mechanism for action but are not identical. The BPCIA has established "highly similar" and "interchangeable" designations for biosimilars, but the Food and Drug Administration (FDA) has not issued any formal recommendations about the latter.[13] Although the FDA recently approved the first biosimilar in the United States, many key regulatory issues are still being debated.

Fast Facts

- The first biosimilar was approved in the United States in March 2015. Express Scripts predicts that this biosimilar, Sandoz's Zarxio, a biosimilar of Amgen's Neupogen, could save the health system $6 billion over the next decade.[1]
- The Biologics Price Competition and Innovation Act (BPCIA) created an expedited licensure pathway, section 351(k) of the Public Health Services Act, for biosimilar approval; most biologics were originally licensed through the traditional 351(a) pathway, which requires comprehensive data and does not rely on findings for any other pharmaceutical approved by the Food and Drug Administration (FDA).[2]
- In Europe, the price of some biosimilars is 20 to 30 percent below the price of biologics.[3]
- The American Enterprise Institute and AARP estimate that research and development costs for reference (or original) biologics average $1.2 billion,[4] but can range from an average of $953 million to almost $6 billion, according to the Innothink Center for Research in Biomedical Innovation.[5]
- Reference biologics in the United States are eligible for a 12-year market exclusivity period.[6]
- A 2011 survey conducted by the National Comprehensive Cancer Network found that 27 percent of health care providers indicated a high interest in prescribing biosimilars, while 35 percent indicated a moderate interest.[7]

What are Biosimilars?

Biologic drugs, also known as biopharmaceuticals, were created to imitate proteins, complex molecules responsible for carrying out most of the functions of our body. They comprise immune response, maintain metabolism, transfer hormonal signals and carry out a variety of other vital tasks. Biologics

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are used to treat a wide range of conditions including cancer and autoimmune diseases. They can also be used as therapeutic vaccinations to prevent disease.[14] Biologics are derived from living organisms and lack well-defined identical characteristics due to their complexity.[15]

The first biologic drugs appeared on the market in 1982, and patent applications for new pharmaceuticals have grown significantly since then. These pharmaceuticals are created using recombinant DNA, a process that combines DNA from multiple living organisms to form the pharmaceutical molecule. The first biologic drug to hit the market, insulin, was created using human insulin and E. coli.[16]

Due to the complexity of reference biologic drugs, their biosimilars are not identical and therefore not considered generics. Unlike small-molecule generics, biosimilars could have a different chemical structure from their biologic counterpart. The biosimilar must establish biosimilarity through analysis of clinical trials, produce the same clinical result, have the same mechanism for action, and indications must be properly labeled. Producers must also demonstrate quality, efficacy and safety.[17] [18]

In March 2015, the FDA approved a biosimilar of Amgen's Neupogen (filgrastim), Sandoz's Zarxio (filgastrim-sndz), making it the first of its kind to get the federal stamp of approval. Neupogen, and now Zarxio, are used to treat Neutropenia, a white blood cell deficiency caused by chemotherapy. As of June 2015, Hospira and Celltrion's biosimilar for Johnson and Johnson's Remicade was also under consideration by the FDA.[19] Neupogen costs $3,000 for 10 injections, whereas Zarxio is expected to cost at least $1,000 less.[20]

Cost and Access

On average, biologics are 22 times more expensive than small-molecule drugs, creating the potential for cost savings via the introduction of biosimilars. The Congressional Budget Office predicts that the first U.S.-approved biosimilar could save payers and patients $6 billion over the next decade by creating competition.[21]

The American Enterprise Institute (AEI) estimated in 2011 that average research and development (R&D) costs for a biologic are $1.2 billion.[22] [23]A more recent study, conducted by Tufts in 2014, calculated the average at closer to $2.5 billion. Both estimates incorporate the costs of drug failure and capital.[24] The R&D process for traditional medications requires about three to six years of drug discovery and preclinical trials, followed by six to seven years of clinical trials.[25] In contrast, according to one biosimilar firm, biosimilars take about eight to 10 years total to research and develop, and have an R&D cost of around $100 million to $200 million.[26] Biologic manufacturers have expressed concern that this market exclusivity time frame is not long enough to recover R&D costs.

Market Exclusivity and Regulatory Issues

In the United States, biologics are eligible for a 12 year market exclusivity period during which competitors cannot begin marketing biosimilars approved by the FDA. This period begins after the date of first licensure, unlike the 20 year patents[27] that apply to small molecule pharmaceuticals. For them, the patent clock starts ticking from the filing date of the application.[28] Often, small molecule generics are able to hit the market as soon as the originator patent expires. However, due to this biologic exclusivity period, biosimilars are not able to do the same. Recent proposals by the Obama administration would reduce this to seven years.[29] Some consumer advocates also support these proposals, contending that decreasing the exclusivity period could lower costs without disincentivizing innovation.[30] However, the pharmaceutical industry contends that the longer exclusivity period is needed to ensure adequate return on investment.[31]

Policymakers also are debating other regulatory issues, including the naming of biosimilars, the conditions under which pharmacists may substitute them for biologics, the approval of biosimilars for multiple indications without additional testing, and reimbursement for biosimilars.

- Naming. Small molecule generics use the same nonproprietary name, a generic name either approved or recommended by the FDA, as the branded product. However, since the biosimilar and originator are not identical, giving them the same nonproprietary name would be misleading. Others counter that a separate brand name and new nonproprietary name for a biosimilar, compared to the reference product, could lead to confusion for consumers, result in lower up-take rates, and hinder competition. In Europe, biosimilars have the same international nonproprietary name as the original, but different brand name and batch numbers.[32]

  In the case of Zarxio, the placeholder of "filgrastim-sndz" has been used by the FDA. The agency expects to issue guidance on naming in the near future.[33]

- Substitution. The BPCIA has established "highly similar" and "interchangeable" designations for biosimilars, but the FDA has not issued any formal recommendations about the latter.[34]

  In addition, the BPCIA does not address whether pharmacists should have to inform

physicians when a biosimilar equivalent is substituted for a given biologic drug. Some states are establishing their own regulations about substitution and notification. State regulators have the ability to decide whether a patient has to consent to the substitution, if the pharmacist is required to inform the prescriber, and what written records need to be maintained by the pharmacists and the provider.[35] Though smaller biotech companies creating biosimilars oppose notification, larger companies that have patented biologics support it.[36]

- Extrapolation. Extrapolation is the approval of biosimilars for multiple indications without additional testing. In some cases, indications for biosimilar drugs are derived from the clinical trials for the original biologic.[37] The BPCIA created an expedited licensure pathway, 351(k), for biosimilar approval, whereas most biologics were originally licensed through the traditional 351(a) pathway, which requires comprehensive data and does not rely on findings for any other pharmaceutical approved by the FDA.[38] The FDA has allowed extrapolation for the first biosimilar approved in the US, but each pharmaceutical will be analyzed on a case by case basis. Official guidance issued by the FDA states, "If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for the biosimilar product to be licensed for one or more additional conditions of use for which the reference product is licensed."[39] Extrapolation is controversial, as some question its effect on safety and efficacy. However, if a biosimilar is able to demonstrate a high level of similarity to its originator, extrapolation is the quickest way to get it on the market.[40]

  For example, in Europe and Asia, indications for Inflectra/Remsima (infliximab) were determined by establishing similarity to the originator product, Remicade. Because Remicade was approved for treating ankylosing spondylitis, rheumatoid and psoriatic arthritis, psoriasis and inflammatory bowel disease, so was its biosimilar. Despite small structural differences between the drugs, tests demonstrated efficacy.[41] However, this might not be the case for every biosimilar; depending on how similar it is to the originator and whether or not small structural differences contribute to the mechanism for action for specific indications, according to regulators and patient groups.

- Reimbursement. The Centers for Medicare and Medicaid Services (CMS) has issued several guidelines on reimbursement for biosimilars through Medicare and Medicaid. In guidance issued in March 2015, CMS asserted that reimbursement would be the average sales price (ASP) for the biosimilar in addition to 6 percent of the ASP of the originator drug, to reduce incentives for prescribing more expensive biologics for Medicare Part B. For the biosimilar Zarxio, CMS created a new healthcare common procedure coding system to distinguish between the biosimilar and the originator drug.[42] Another document addressing formularies for Part D stated, "the reference and biosimilar products will not be considered as different drugs for the purposes of satisfying the two distinct drugs requirements for each of the submitted categories and classes."[43]
- International Comparisons. The United States currently lags behind other nations that have already introduced biosimilars to their markets.[44] For example, the European Union (EU) started approving biosimilars in 2006, and 22 biosimilars have been approved there to date.[45] [46] The market share for biosimilars in Europe continues to rise after introduction of biosimilars resulted in an average of 20 to 30 percent price drop for some biologics.[47]

  Drug prices and biosimilar take-up rates vary among nations, at least in part driven by different policies in different countries. For example, a study conducted by the IMS Institute for Healthcare Informatics found that market penetration for a biosimilar of Erythropoietin (EPO) varied greatly across European nations. Since its launch in 2006, market penetration, calculated based on market share of the biosimilar compared to the reference biologic, ranged from 1 percent in Croatia to 62 percent in Bulgaria. Increase in patient access to access to biosimilars in the EPO market ranged from a 17 percent growth in Poland to a 96 percent growth in Denmark. This was calculated by determining the percentage of total treatment days for which EPOs are used, indicating increased access. They determined that these differences were not due to epidemiologic factors, but to local regulations about treatment and payer practices as well as funding. For example, substitution incentives and physician awareness lead to higher take-up rates and greater price competition.[48]

Resources

Comparing Biologics and Biosimilars

Biologics and Biosimilars: An Overview
Amgen. March, 2014
http://goo.gl/0PBrVv
This overview explains differences between biosimilars and generics, the regulatory process, and discusses issues with naming and substitution. Over the next few years, patents for many biologics, worth approximately $81 billion in international sales, will expire, creating an opening for biosimilars to enter the market.

Biosimilars
Elizabeth Richardson. *Health Affairs*.
October 10, 2013
http://goo.gl/BlPwms
This issue brief describes biosimilars, outlines key policy issues, and discusses the regulatory process. It also describes potential outcomes for current proposals and what some claim are Biologics Price Competition and Innovation Act (BPCIA) market exclusivity loopholes. The author concludes that Food and Drug Administration (FDA) regulations will ultimately determine the extent to which a biosimilar is able to penetrate the pharmaceutical market in the United States.

Small Molecules or Biologics?
Jean-Claude Muller. BtoBio Innovation. April, 2013
http://goo.gl/WQmJFF
This brief describes the difference between small molecule drugs and biologics, as well as provides some insight into how biologics are created. It addresses the efficacy and economic implications of biologic pharmaceuticals, emphasizing that they are revolutionary for the treatment of chronic disease.

Developing Biosimilars
Hospira. October, 2013
http://goo.gl/tES5jM
This document describes the difference between the drug development processes for biologics and biosimilars. The research and development process for biologics requires about three to six years of drug discovery and preclinical trials, followed by six to seven years of clinical trials. In contrast, biosimilars take about eight to 10 years total to research and develop and cost around $100 million to $200 million, compared to $1.2 billion for reference biologics.

Why Are Biologic Drugs So Costly?
Glover, Lacie. U.S. News. February 6, 2015
http://goo.gl/oaqdOX
This article discusses reasons behind the costs of biologic pharmaceuticals. The author points to monoclonal antibodies, which are highly targeted treatments designed to work with the immune system, and says that they are the most expensive and rapidly growing biologic pharmaceutical.

Biosimilars and Interchangeable Biologic Products the Next Frontier for Improved Access to Medicines
Generic Pharmaceutical Association (GPhA). June, 2015
http://goo.gl/75jEXF
This handbook highlights why biosimilars and interchangeable biologic products are important for improving access to care and lowering costs. It describes how patients, taxpayers, employers and governments could benefit and provides examples of the impact of biosimilar introduction to the European market. The regulatory framework in the United States is also outlined.

Pharmaceutical Market

Assessing Biosimilar Uptake and Competition in European Markets
IMS Institute. October, 2014
http://goo.gl/maUfNr
The report details a study conducted by the IMS Institute on changes to the European pharmaceutical market after the release of biosimilars for Erythropoietin (EPO), Human Growth Hormone (HGH), Granulocyte colony-stimulating factor (G-CSF), and Anti-Tumor Necrosis Factor (Anti-TNF) since their launch in 2006. The authors observed biosimilar penetration into the market drug prices, access to innovation for specific pharmaceuticals, treatment consumption, and overall medical costs in 22 different nations, and determined that variation in these areas were not due to epidemiologic factors, but to local regulations about treatment and payer practices, as well as funding.

FDA Decision Signals New Competition For Some Of The Costliest Drugs
Elana Gordon. NPR. March 10, 2015
http://goo.gl/E4Nvpa
The article discusses FDA approval of the biosimilar for Amgen's Neupogen, known as Sandoz's Zarxio, the first of its kind in the United States. Express Scripts estimates that Zarxio alone could save approximately $6 billion over the next decade, based off of cost savings that resulted from the introduction of biosimilars to the European market.

Cost of Developing a New Drug
Henry G. Grabowski and Ronald W. Hansen. Tufts Center for the Study of Drug Development. November 18, 2014
http://goo.gl/meLs2y
This presentation explores high research and development costs for biologic pharmaceutical manufacturers through a study conducted by Tufts Center for the Study of Drug Development. The study found the drug development has a pre-tax average cost of $2.5 billion, including failures and capital costs. The data set looked at new drugs created by pharmaceutical firms through 2013.

Biologics in Perspective: The New Biosimilar Approval Pathway
Leigh Purvis. AARP Public Policy Institute. October, 2011
http://goo.gl/ypm5vB
This fact sheet explores the drug approval pathway created by the Affordable Care Act (ACA) as well as its potential impact on pharmaceutical costs. It notes that global drug prices are steadily increasing and research and development costs for reference biologics average $1.2 billion per drug.

Drug Patents Pose a Major Hurdle to Pacific Trade Deal
William Mauldin. *The Wall Street Journal*. Feb, 2015
http://goo.gl/H8GSxa
This article discusses disagreement over the 12 year exclusivity period for biologics in the Trans-Pacific Partnership trade agreement. Many of the countries involved in the trade agreement have much shorter exclusivity periods and are opposed to a12 year exclusivity period.

Regulatory Issues

Biologics Price Competition and Innovation Act of 2009
FDA. 2009
http://goo.gl/d1jsfh
This document from the FDA contains the full text of the BPCIA, which was part of the Affordable Care Act under Title VII—Improving Access to Innovative Medical Therapies.
A summary is also available here:
http://goo.gl/U2tUcH

CMS Issues Guidance on Reimbursement for Biosimilars under Medicare and Medicaid
King & Spalding. April 15, 2015
http://goo.gl/SU1Oxr
This document describes new guidance issued by the CMS that addresses Medicare Parts B and D, and also the Medicaid drug rebate program. In the case of Zarxio, CMS created a new Healthcare Common Procedure Coding System ("HCPCS") code to distinguish between the biosimilar and the originator drug.

CMS Provides Guidance on Reimbursement and Formulary Policies for Biosimilars
Randi Hernandez. BioPharm International. April 1, 2015
http://goo.gl/w5d3Hp
This article discusses a new CMS document that the author notes would reduce the incentives for physicians from prescribing expensive biologics once a biosimilar becomes available. Reimbursement would be the average sales price (ASP) for the biosimilar in addition to 6 percent of the ASP of the originator drug. CMS also issued guidance on formulary requirements for Medicare's prescription drug program (Part D) and state Medicaid drug rebates, stating that the reference and biosimilar products will not be considered as different drugs for the purposes of satisfying the two distinct drugs requirements.

Senate Health Committee Republicans Urge FDA to Provide Clarity, Certainty on Biosimilar Drug Approval Process
Margaret Atkinson and Jim Jeffries. US Senate Committee on Health, Education, Labor & Pensions April, 2015
http://goo.gl/bdxhoN
This document presents a letter from nine Republican Senators, arguing that the FDA should finalize long-awaited guidance on biosimilars. The senators state that, without clear guidance on approval pathways, the safety and efficacy of biosimilars is called into question.

Food and Drug Administration Approval of First Biosimilar Product
Centers for Medicare & Medicaid Services. March, 2015
http://goo.gl/M474bL
CMS addresses questions for Medicare beneficiaries after FDA's approval of Zarxio, the first biosimilar approved in the United States. CMS addresses questions about reimbursement under Medicare Part B, coding and Part D.

Biosimilar Competition in the United States: Statutory Incentives, Payers, and Pharmacy Benefit Managers
Benjamin P. Falit, Surya C. Singh and Troyen A. Brennan. *Health Affairs*. February. 2015
http://goo.gl/Mg7eJd
This article analyzes key differences between the Hatch-Waxman Act of 1984 and the Biologics Price Competition and Innovation Act (BPCIA), which respectively regulate generics and biosimilars. They FDA has still not worked out many of the regulatory guidelines for biosimilars, even years after the enactment of the BPCIA. As a result, there may be variation in what evidence is required for approval, they authors indicate. Regulatory obscurity and unclear criteria for biosimilar and interchangeable designations will impact whether biosimilar manufactures pursue approval through the abbreviated pathway.

Why Doctors Need To Know When Pharmacists Substitute Biological Medicines
David Charles and Mary Ann Chapman. Institute for Patient Access. January, 2014
http://goo.gl/3Annt4
The authors maintain that prescribers should be notified when pharmacists substitute a biosimilar for a biologic drug, to assess whether a biologic or its biosimilar produced specific side effects.

A Sense of Déjà Vu: The Debate Surrounding State Biosimilar Substitution Laws
Leigh Purvis AARP Public Policy Institute. September, 2014
http://goo.gl/ffBWAQ
This issue brief discusses the impact of biosimilars on the price of biologic drugs. The BPCIA did not address regulatory issues such as substitution, so states might have to decide key regulatory policies, according to the brief. State regulations, for example, may address whether a patient has to consent to the substitution, if the pharmacist is required to inform the prescriber, and what written records need to be maintained by the pharmacists and the provider.

The Pharmaceutical Industry Tussles Over Biosimilars
Stephen Barlas. National Center for Biotechnology Information. April, 2014
http://goo.gl/3vLnV4
This article discusses the impact of federal and state decisions on the biosimilar pharmaceutical market. It addresses such decisions as substitution, tracking and cost. Though smaller biotech companies creating biosimilars oppose notification, larger companies that have patented biologics support it, they state.

FDA Releases Guidelines for 12- Year Period of Reference Product Exclusivity for Section 351(a) Biologics
Timothy J. Shea, Jr. *The National Law Review*. August, 2014
http://goo.gl/zjpAmB
This article explains FDA guidelines clarifying that the FDA will not approve biosimilars under the 351(k) application pathway until 12 years after the date on which the reference product was licensed.

Obama Budget Blueprint Seeks Drug Pricing Authority, Shortened Data Exclusivity Period for Biologics
Randi Hernandez. BioPharm International February 2, 2015
http://goo.gl/WFWe65
This article outlines the Obama administration's plans for pharmaceuticals in the 2016 budget, including proposals to lessen the exclusivity period for biologic drugs from 12 years to 7 years and give the secretary of Health and Human Services the ability to negotiate pharmaceutical prices for Medicare Part D.

Biosimilar Substitution
National Psoriasis Foundation. February 10, 2015
https://goo.gl/SjP3zO
This position statement by the National Psoriasis Foundation outlines recommendations for biosimilar substitution to ensure safety. Since biosimilars are not identical to their reference biologic, the organization states, proper naming, dosage, route of administration and notification regulations are key to guaranteeing patient safety standards are being met.

Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009
FDA. May, 2015
http://goo.gl/DEXXWo
This Q&A draft guidance released by the FDA addresses biosimilarity, interchangeability, and market exclusivity for the pharmaceutical industry. The document also details dosage, labeling and extrapolation.

American Autoimmune Related Diseases Association Letter to FDA
AARDA. May 13, 2015
http://goo.gl/19ujNA
This letter from AARDA urging the FDA to issue guidance on naming emphasizes patient safety. Since the treatment of autoimmune disorders poses many risks, according to the letter, it is important to have clear distinction between similar and identical products, as well as to have the ability to disaggregate data.

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; General Licensing Provisions; Section 351(k) Biosimilar
FDA. July, 2015
https://goo.gl/eyTFtL
This pending FDA guidance on interchangeability describes what is necessarily for a biologic product applying for licensure through the abbreviated pathway to be considered an interchangeable drug.

Doctors Unwilling to Trust Similarity of Biosimilars
Onclive Strategic Alliance Program May 13, 2015
http://goo.gl/ikexJJ
This article outlines provider skepticism about whether biosimilars would be perfect substitutes for their reference biologics and the need for proper safeguards to ensure patient safety. The piece goes on to talk about provider notification if a drug is substituted and ongoing debate surrounding Zarxio.

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www.allhealth.org

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