

Understanding Biologic Medicines From the Cancer Patient Perspective

January 2013

Table of Contents

Table of Contents	2
Executive Summary	3
Scientific and Clinical Considerations for Biologics and Biosimilars	4
Traditional Small Molecule Drugs Have a Long History of Generic Alternatives	4
Biologic Medicines Are Usually Larger and More Complex than Small Molecule Drugs	4
What Are Biologics?.....	6
Biologic Therapies Play an Important Role in Cancer Treatment	8
Manufacturing Biologics versus Traditional Pharmaceuticals.....	11
What Are Biosimilars?.....	13
Biosimilars Are Not Exact Copies of Originator Biologics	14
There are Safety and Efficacy Concerns Inherent to Biologic Medicines	15
Marketplace and Cost Considerations Creating Demand for Biosimilars	17
Policy Considerations for Biosimilars: Emerging Stakeholder Issues	20
FDA Has an Established Process to Regulate Biologic Therapies	21
FDA Is Establishing Its Pathway to Regulate Biosimilar Products.....	22
FDA Is Establishing Criteria for Manufacturers to Demonstrate Biosimilarity	23
FDA Will Determine When Biosimilars Can “Extrapolate” Additional Indications.....	24
An FDA Interchangeability Designation has Implications for Substitution.....	24
FDA Will Affect Access to Biosimilars, Beyond Scientific Pathway Considerations.....	26
Biosimilar Manufacturers Will Need to Pay User Fees During Development.....	26
Naming of Biosimilars Coming Under Increasing Scrutiny in the Debate of Patient Safety....	27
Payer Reimbursement for Biologics and Biosimilars Will Affect Patient Access.....	28
U.S. States May Have Additional Authority in Determining Access to Biosimilars.....	28
Potential Opportunities for Stakeholder Education	29
Conclusions	30
Appendix	31
Medicare Coverage and Payment of Biologics, in Particular the Role of Part B and Part D.....	31
Medicare Part B Coverage.....	31
Medicare Part B Payment	32
Medicare Part D	33
Private Insurance Medical Benefit Drug and Biologic Coverage	34
Private Insurance Pharmacy Benefit Drug and Biologic Coverage.....	35

Executive Summary

Biologics are essential for cancer treatment, both in addressing the underlying disease and in offering supportive care to patients undergoing treatment. In March of 2010, as part of the Patient Protection and Affordable Care Act (ACA), Congress gave the Food and Drug Administration (FDA) the authority to develop a pathway to approve biosimilar medicines - products that are highly similar to currently available, brand-name biologics. Similar in concept to generic drugs, biosimilars are an opportunity to expand patient access to lower-cost treatment options that are likewise subject to FDA approval. While biosimilars will potentially become available for many diseases, including cancer, patient access to these products will ultimately depend on the actions of the FDA, physicians, pharmacists, and payers, as well as the companies that invest in making them.

In this paper, we explore the important roles that the FDA, physicians, and health insurers will play in making sure cancer patients have timely access to all available treatment options, and the potential impact of these decisions on the cost of treatment for patients. The FDA will decide which products become available to patients because they will define the data needed for approval of biosimilar products. Physicians will decide what to prescribe to each patient, and in many cases what specific product to administer, such as in the case of an in-office infusion. For self-administered products, pharmacists responsible for dispensing products will be able to help patients to understand if there are lower-cost alternatives available, including biosimilars. However, local state law will govern pharmacists' ability to automatically substitute biosimilar products the FDA says are interchangeable with their reference product. Finally, the policies that payers – Medicare, Medicaid, and private health insurance companies – implement around patient cost sharing, physician reimbursement, formulary structure, and product coverage will also help shape the biologic and biosimilar market, and ultimately patient access to treatments of all kinds.

ACS CAN commissioned this primer to provide an educational overview of the key scientific and policy issues facing the evolving biologics/biosimilars therapy landscape. However, please note that this document does not necessarily reflect, nor does it intend to endorse, the official positions of the organization.

Scientific and Clinical Considerations for Biologics and Biosimilars

Traditional Small Molecule Drugs Have a Long History of Generic Alternatives

The development of small molecule drugs for the treatment and prevention of disease has played a pivotal role in the practice of medicine during the last century. The availability of these drugs to control infections, manage chronic diseases, and to increasingly, treat cancer, has contributed to improvements in both public health and life expectancy. The most familiar type of small molecule drug is the pill taken by mouth that contains a single chemical drug, like aspirin. A synthesized small molecule drug is a substance made entirely from chemical reactions between different organic or inorganic compounds in a laboratory. A small molecule drug, such as aspirin, is structurally straightforward, and a different manufacturer could easily reproduce or duplicate such a therapy (see Figure 1 below).

When small molecule drugs receive FDA approval, they do not have risk of direct competition based on patent protection—20 years from patent filing. Separate from patent protection, drugs have a period of exclusivity from FDA approval of a new drug (known as a new molecular entity or NME) and lasts for up to five years. Exclusivity is a period to sell the drug without direct competition from a duplicate product because FDA will not approve a competing drug in that time, but it often runs concurrently with the patents. However, when both the patent and the exclusivity expire, different manufacturers can produce and sell “copies” of the drug, known as generics. These are often available at a deeply discounted price.

Approval for generic drugs relies on the prior FDA finding of safety and efficacy for the chemical in the original brand drug, and so clinical trials for generics are not necessary. This reduces the cost of pre-approval testing, and the manufacturer can pass those savings on to patients. Generic manufacturing, price competition and generic utilization have been increasing at a rapid pace. All generic manufacturers must show that the generic product’s active ingredient—the substance within the drug that actively performs the drug’s specific function—contains the identical chemical composition of the brand product. The generic’s information (data) must also show similar rates of absorption and activity within the body (known as bioavailability studies showing similar pharmacokinetic properties). Since the introduction of generic drugs, patient access to products just as safe and effective as brand therapies has dramatically increased.

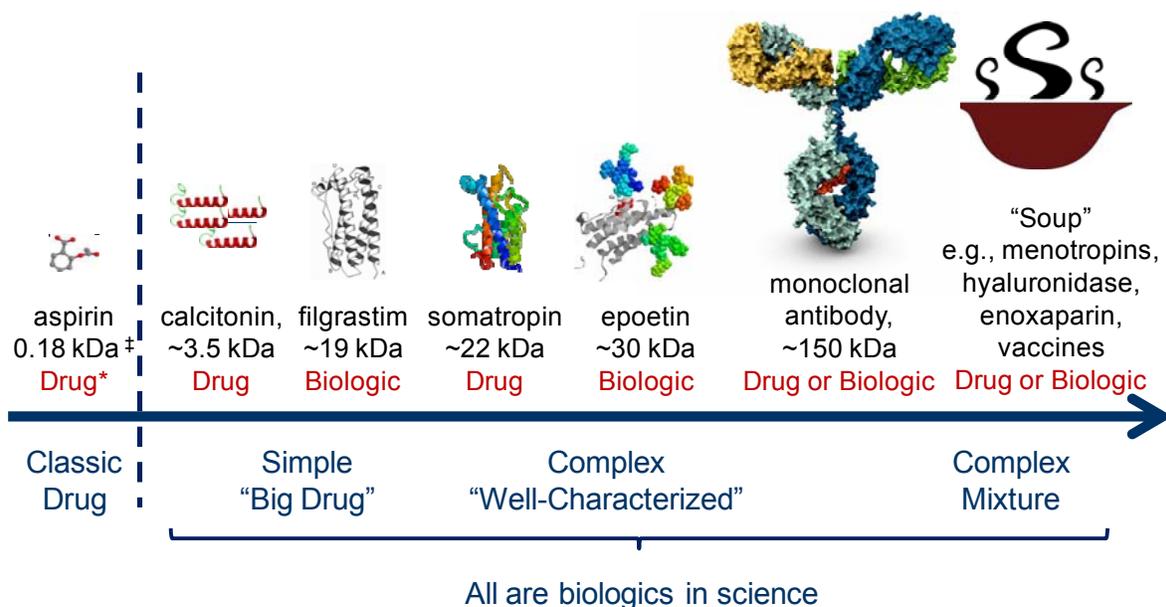
Biologic Medicines Are Usually Larger and More Complex than Small Molecule Drugs

While biological products, such as vaccines, have been available for centuries, modern technology has allowed a whole new area of research to contribute to the development of medicines. As we increasingly understand diseases and their progression, researchers began developing another type of precision medicine based in biology to target specific elements in the human body affecting disease. In the past several decades, biologic products have emerged as

increasingly important treatments, allowing medicines that work with remarkable biological precision and often with far fewer side effects than chemical drugs.

Biologics now provide leading therapies essential in treating conditions like cancer and autoimmune disorders.¹ A class of biologic therapies known as monoclonal antibodies (discussed in more detail later and shown in Figure 1 below) targeting oncology alone accounts for over 14 percent of total U.S. spending on biologics.² For oncology, the special properties of biologics result in precise targeting of cancer cells individually (unlike surgery which, while still extremely important, is far less precise), enabling better clinical outcomes while minimizing debilitating adverse effects. Biologics frequently have substantially fewer toxic side effects than many small molecule drugs. This targeted approach allows these biologic medicines to provide the best options for effective treatment of diseases that are difficult to treat, like cancer. Often biologics complement other therapeutic approaches, and cancer patients need the epitome of individual patient-centered care. Timeliness in access is also critical to optimal outcomes.

Figure 1: Continuum of Small Molecule and Biologic Therapies in Size and Complexity



*Drug/Biologic = Regulatory pathway used by FDA for their original approval (unique to US)

[‡]Da =Dalton, a metric unit used to measure the size of a molecule

¹ McCamish, Mark. The Clinical and Financial Impact of Biosimilars. Health Reform 2012. Available at http://www.cdmihealth.com/CDMI_Journal/Fall_2012/index.html#/40/zoomed. Last accessed November 9, 2012.

² IMS Health. Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape. Available at http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_Whitepaper.pdf. Last accessed November 8, 2012.

What Are Biologics?

Biologic products are often 200-1000 times larger than traditional small molecule drugs, (see Figure 1 above). Biologics do not result from simple chemical processes like small molecule drugs; instead they use living cells, and this enables much greater complexity in structure than traditional small molecule drugs. However, just like small molecule drugs, biologic medicines can prevent and treat a variety of diseases and health conditions. Biologic products include vaccines, blood and blood products, proteins, gene and cell therapies. Many of the most important and commonly used biologics are proteins. Proteins are a type of molecule made up of chains of amino acids that come in multiple shapes and sizes. They are normally produced in our bodies, give our cells structure, and tell our cells what to do and how they should function.

Proteins are sensitive to the conditions and environment of creation—both naturally and when manufactured as medicines—often leading to natural variations between protein molecules. This creates individual molecules that are often not identical to one another and, when used in medicines, can vary such that biologics represent complex mixtures even within a single vial. For this reason, biologic manufacturers dedicate significant resources to ensure that they manufacture biologic medicines in a carefully controlled and consistent manner so that they behave predictably in all patients with every administration. As with any medicine, deviation in the manufacturing process may affect the final product's structure and, therefore, its safety and efficacy. Consequently, the FDA licenses all facilities that produce biologics used in the U.S. and any manufacturing changes to biologics are subject to careful oversight by the FDA.

Biologics can be isolated from many sources— including humans, animals, and microorganisms grown in cultures in laboratories. Historically, biologics such as insulin came from natural animal sources (see Figure 2), and vaccines came from modified strains of bacteria and/or viruses. While many of these techniques have been replaced by biotechnology (see following paragraph), it is important to note that natural sourcing is still an important part of the supply of biologics—for example, blood transfusions, intravenous immunoglobulin (IVIG), or some hemophilia clotting factors.

In 1982, “recombinant” (which means scientifically recombined, also sometimes called genetically engineered) human insulin became the first biologic medicine to gain FDA approval.³ Since this first success, recombinant techniques have yielded replacement human proteins and even a few “designer biological molecules” not found in nature.⁴ This technology entails the insertion of select genes into cell lines grown in cultures to manufacture molecules with specific qualities. Other techniques can prompt the cell to produce the protein in an optimal manner for that needed for treatment and tailor the protein to address particular disease processes – hence creating molecules never before seen in nature (see Figure 2). Once isolated, these proteins

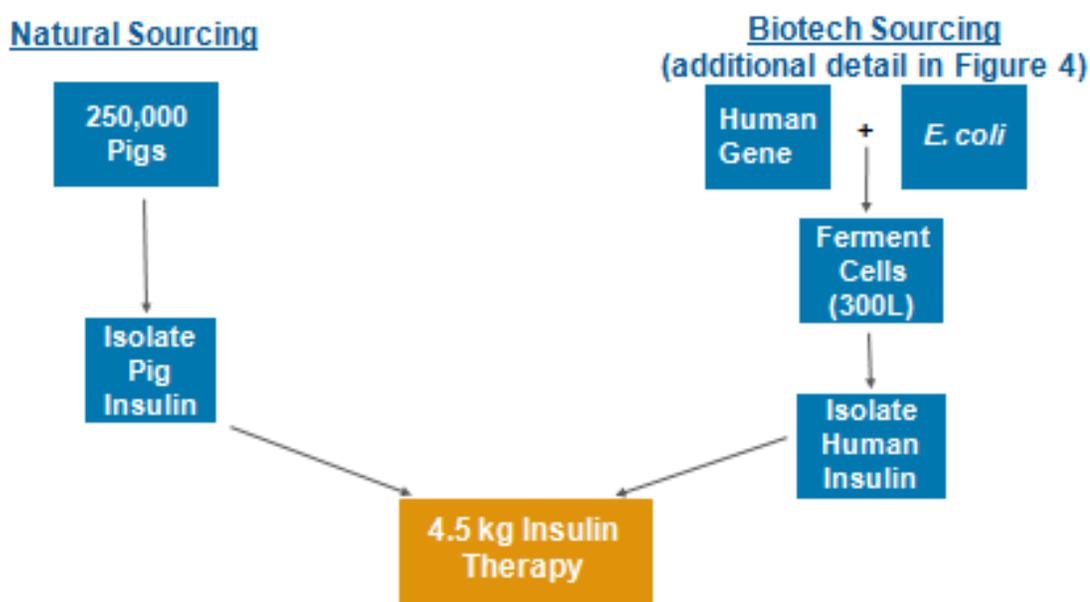
³ FDA. *Celebrating a Milestone: FDA's Approval of First Genetically-Engineered Product*. Available at <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SelectionsFromFDLIUpdateSeriesonFDAHistory/ucm081964.htm>.

⁴ FDA. *Celebrating a Milestone: FDA's Approval of First Genetically-Engineered Product*. Available at <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SelectionsFromFDLIUpdateSeriesonFDAHistory/ucm081964.htm>.

are the active ingredients in medicines, usually administered by injection or infusion as the molecules are too fragile for oral administration.

While typically referred to as more complex than small molecule drugs, biologic therapies vary greatly in complexity. Some biologics are essentially “large drugs” whereas others contain bigger molecules that are inherently complex mixtures. Therapies can also vary in complexity based on cells used for their creation (e.g., bacterial cells produce simpler molecules, generally speaking, than yeast and mammal cells). Most biologics require administration as either an injection (under the skin) or as an infusion (in the vein). This has traditionally been because when taken orally, large proteins are too large for absorption by the body. However, manufacturers have recently developed oral biologics in order to facilitate ease-of-use for patients self-administering these products at home. These are still rare.

Figure 2: Recombinant Biotechnology Has Increased Availability of Biologic Therapies



Due to their generally larger size and often more complicated structures, it can be difficult to identify and define all components of the molecule’s structure. However, improved scientific analytical techniques now available increasingly allow “molecular fingerprinting”—full mapping—for many biologics to a level of detail not previously possible. This is important because it allows biologic manufacturers to ensure that each batch of their biologic product is comparable to the product initially studied/launched, even when they change its manufacturing conditions. This helps assure similar patient benefits when administering the medicine in a real-world setting. Nonetheless, the process of creating safe and effective medications from these large complex proteins is still complicated and requires dedicated facilities to ensure maintenance of high quality standards. The complex nature of biologic manufacturing is one reason why these medicines can be costly.

Biologic Therapies Play an Important Role in Cancer Treatment

Biologic therapies are important in oncology treatment. They work by using a patient's own immune system either directly or indirectly to fight cancer, thereby either targeting cancer cells for destruction or reducing the side effects from chemotherapy or radiation.

The immune system is an intricate network of cells, tissues, and organs that work together to defend the body from disease and infection by fighting unfamiliar invaders such as bacteria or viruses. The immune system also can distinguish between normal cells and cancer cells, most of the time working effectively to help the body eliminate such unwanted cells. However, when the immune system does not recognize cancer cells as “foreign” or when the immune system is under stress and not functioning properly, cancer cells may escape detection and flourish. Disease then results.

Biologics work in oncology by selectively targeting specific aspects of cancer cells. As a result, when used for cancer treatment, biologics do not kill as many healthy cells in the body and thereby result in less toxic, more manageable side effects for the patient. This is one of the main reasons that biologics are so important in the treatment of cancer. Lastly, biologics can be used after other conventional cancer treatments such as surgery, chemotherapy and radiation therapy to further reduce side effects inherent in these treatment options—such as low blood counts, risk of infection, risk of severe fatigue, and risk of bleeding.⁵ All patients need specifically targeted treatments, and it is important that all therapeutic options are available to them in a timely manner.

After decades of research focused on fully understanding cancer cells, including the profiles of cancer cells, their targets in the body, and cancer cell signaling habits, scientists now have a much better understanding of the complex interaction between cancer cells and the human immune system. Using this knowledge, researchers have designed biologic medicines to repair, stimulate, or improve the immune system's response to cancer by stopping, controlling, or diminishing the process that allows the growth of cancer cells. This can mean making cancer cells more recognizable for destruction by the body, altering the growth pattern of cancer cells to encourage healthy growth behavior more like normal cells; blocking or reversing the process that led normal cells to become cancerous; improving the body's ability to replace or repair normal cells damaged by cancer treatments such as during chemotherapy or radiation therapy; or preventing cancer cells from spreading through the rest of the body.

Specifically for cancer treatment, monoclonal antibodies (mAbs) provide some of the most beneficial therapies for both blood-based and solid tumor cancers created in the last two decades.⁶ MAbs are proteins that specifically target cancer cells to help signal the immune system to destroy them. MAbs represent some of the largest, and most complicated biologics used in medicine (see Figure 3). They come from specially cultured cells, and the proteins are

⁵ National Cancer Institute *Cancer Topics: Types of Treatment*. <http://www.cancer.gov/cancertopics/treatment/types-of-treatment>. Accessed December 7, 2012.

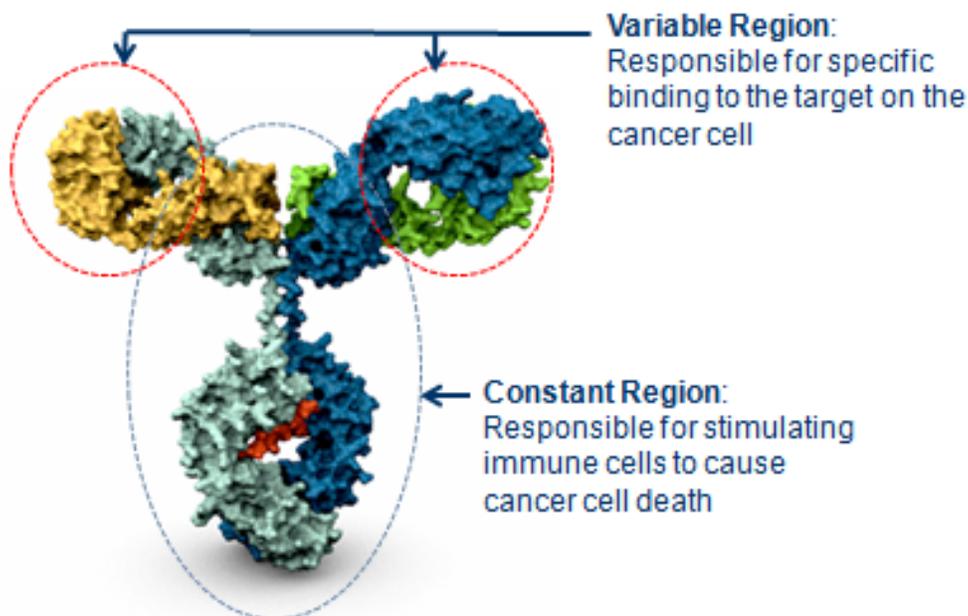
⁶ Scott, AM., Allison, JP., Wolchok, JD. *Monoclonal antibodies in cancer therapy*. *Cancer Immunity* (May 2012). Vol 12, p 14-21.

individually similar (see Figure 1 above), but the medicines that result are unlike the complex mixtures of other antibodies called immunoglobulins that are naturally sourced from donated blood.

Each mAb is specific for a particular antigen, (a component of the cell found on the surfaces of cells such as viruses, bacteria, as well as on cancer cells). Researchers design a so-called “variable region” on the mAb (see Figure 3) molded to fit a particular target. Once the mAb binds to its antigen and/or protein, a separate region of the mAb (known as the “constant region” as shown in Figure 3) very specifically flags the undesirable cell it attaches to for elimination and destruction.

Researchers continue work to further develop mAbs specific to antigens found on the surface of cancer cells to identify more cells for destruction by the patient’s own immune system, with minimal side effects. Monoclonal antibodies are dual purposed, they target antigens involved in cancer cell functioning, and they stimulate the immunologic responses important in limiting cancer disease progression. Examples of mAbs approved by the FDA for use in oncology are Rituxan[®](rituximab), used in the treatment of non-Hodgkin’s Lymphoma and Herceptin[®] (trastuzumab), used in the treatment of some breast cancers.

Figure 3: Monoclonal Antibody (mAb) Structure Suggests Its Role in Cancer Treatment



Biologics not only have treatment roles in the management of cancer patients, but they also serve supportive care functions, such as reducing the side effects of other cancer treatments like chemotherapy and radiation, that can ultimately save lives too. For example, the class of biologics known as colony-stimulating factors (CSFs) does not directly affect tumor cells; they instead encourage stem cells in a patient’s bone marrow to divide and develop into white blood

cells, red blood cells, or platelets, all of which are essential to a healthy immune system and the ability to counter infection. The CSF Neupogen[®] (filgrastim) is useful for many cancer patients receiving chemotherapy, because the chemotherapy drugs can cause a decline in the production of neutrophils (a type of white blood cell) in the bone marrow.⁷ Filgrastim increases the number of white blood cells in the body necessary for fighting off infection, and consequently reduces the risk of infection in those receiving chemotherapy. Likewise, Procrit[®] (epoetin alfa) increases the number of red blood cells in the body, and ultimately reduces the need for red blood cell transfusions in patients who have chemotherapy and radiation therapy induced anemia.

By using these supportive therapies, patients can receive anticancer treatments at more effective higher doses without an associated increased risk of infection or need for blood transfusion. As a result, often patients are able to continue to lead substantially more normal lives with outpatient, rather than inpatient care, due to more manageable side effects, and yet still have better clinical outcome through their ability to tolerate more aggressive cancer treatments. Biosimilars to both epoetin alfa and filgrastim are available in Europe, and multiple other countries, but not yet in the U.S.⁸

Researchers interested in future uses of biologics in the field of oncology are now exploring the use of vaccines to treat cancer patients in clinical trials.⁹ Traditional vaccines (such as the varicella vaccine—chickenpox) work when introduced into the body before development of the disease in order to stimulate an immune response that prepares the body to stop the infection rapidly should that individual subsequently become exposed. Researchers are trying to develop vaccines that similarly stimulate the immune system so that a person can rapidly recognize and kill cancer cells.¹⁰ These cancer vaccines will both treat and prevent cancers (e.g., the recently-approved HPV vaccine prevents multiple forms of cervical cancer).¹¹

Other future uses of biologics include individually targeted cell and gene therapies. Gene therapy entails introducing genetic material, DNA, directly into a patient's own cells in order to fight a specific disease. Researchers are also exploring gene therapies that can enhance a patient's immune response to cancer, such as boosting the ability of the body's immune cells to recognize and attack cancer cells. Biologic therapies, both current and future, help the body's own defense mechanism, the immune system, and identify cancer cells early when they are rare. Then the patient can kill them, avoiding many of the debilitating effects of cancer.

⁷ U.S. Food and Drug Administration. FDA approves new treatment for severe neutropenia in certain cancer patients. Available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317392.htm>.

⁸ Weise et al "Biosimilars: what clinicians should know" *Blood* (October 26, 2012 on line prepublication) 10.1182/blood-2012-04-425744

⁹ Scott, AM., Allison, JP. Wolchok, JD. *Monoclonal antibodies in cancer therapy*. *Cancer Immunity* (May 2012). Vol 12, p 14-21.

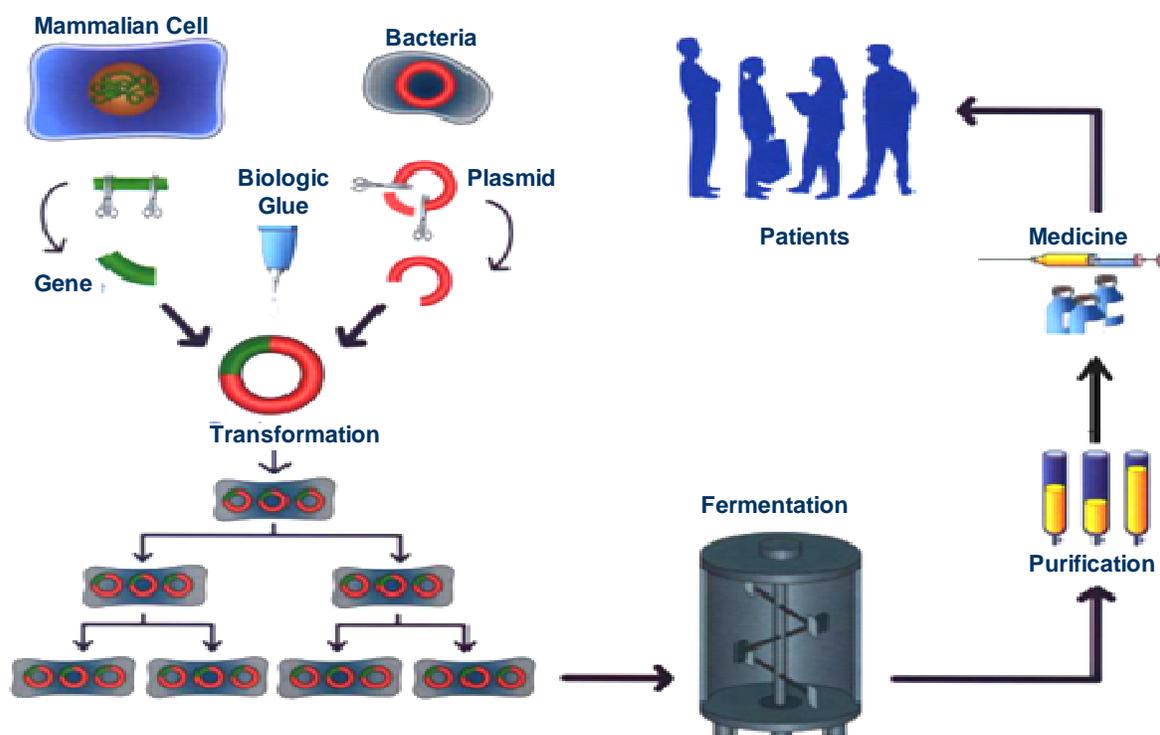
¹⁰ <http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/immunotherapy/immunotherapy-cancer-vaccines>

¹¹ FDA, Center for Biologics Evaluation and Research. Strategic Plan for Regulatory Science and Research 2012-2016. Available at <http://www.fda.gov/downloads/biologicsbloodvaccines/scienceresearch/ucm303542.pdf>

Manufacturing Biologics versus Traditional Pharmaceuticals

One key difference between biologics and small molecule drugs are the source materials used to make them. As previously discussed, biologics come from living sources, while drugs are made from chemicals. Given the different origins of biologics and traditional pharmaceuticals, and the fact that biologics are generally more complicated than small molecule drugs, their manufacturing processes are significantly different as well. Biologics are very sensitive to their environment and the manufacturing process, which explains why even seemingly small change in the manufacturing process, product handling, and container closure (the syringe, stopper, needle) etc., can alter the structure of the product, resulting in products different from one another.¹²

Figure 4: Process of Creating a Biologic Therapy



Biotech biologic medicines begin as genetically modified cell line created by the product manufacturer (see Figure 4 above). First, researchers decide what molecular candidate they are trying to make, and design a generic construct to make it. Then they assemble a cell line that makes the desired protein. Initially most biotech products were replacement human proteins, designed to match the human-sourced original as closely as possible. More recently, biotech products have specific functional attributes from the beginning, and do not necessarily match a previously identified human protein.¹³ This design of the molecule and the creation of

¹² Casadevall N. Immune-response and adverse reactions: PRCA case example. http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500011064.pdf (accessed 4December 2012)

¹³ Examples are Humalog with its shorter half life, and Enbrel which is a fusion protein; mAbs are related insofar as they are selected but not from human sources, historically mouse.

the initial prototype take substantial effort, and many years go into this design of the molecule and the system that will manufacture it. This work becomes the basis of patent protection.

Researchers develop a cell line from the original modified cell, selecting the most stable cell lines based on their ability to reliably produce the protein of interest in high concentrations. Frozen batches of these cells are stored in multiple locations to provide the master cell bank for the biologic medicine. Manufacturing a biologic medicine entails thawing and growing batches of these cells into the working cell bank to produce the desired protein, which becomes the "active ingredient" for the medicine. Then, the manufacturer separates and purifies the protein from the cells and formulates it into the final product. The formulated product goes into vials or syringes for use by providers and patients. Biologics, unlike drugs, have the additional challenge that almost every manufacturing step must take place in sterile conditions.

Historically, biologics were believed to follow the concept of "product is process," a theory assuming that if a manufacturer keeps the raw starting materials and the manufacturing process the "same," then the resultant product will be the "same" too. However, this idea was not always correct because many biologics, especially those from natural sources, still showed some variability, and the nature of biologics means that one often has multiple types of molecule even within a single batch of product. The introduction of recombinant biotechnology has enabled greater consistency through deriving each batch from a single cell line. In addition, modern analytics allow for better identification of variations between different batches of products, or the same batches over time (which help determine the allowable shelf life and expiration dates of these medicines—a product's stability).

Biologics can be extremely complex structurally, and this is important for patients because any twists, turns, and kinks in the structure of biosimilars that vary can cause the patient's immune system to determine the product is a foreign substance and mount an immune response. A different cell line, source of raw materials and environment for reproducing cells can all affect the final product. While not all of these differences matter, the goal is to know which differences do matter. This information is often limited during the product's pre-approval periods, and therefore it is essential to monitor the product's performance in the real-world setting after approval to ensure the safety and efficacy of the biologic and pick up rare unusual reactions (even for small molecule drugs it is difficult to detect rare events pre-approval).

Because of the potential for variability, a great deal of care is necessary throughout the manufacturing process of every biologic to ensure a consistent product each time. Variations in biologics can influence cell behavior and produce proteins that are not identical copies of one another and the concern is that some of these molecules will not have the same clinical outcomes as others when introduced into patients. This process has to be as uniform as possible so that medicine will behave predictably in each patient with each administration. Even small changes in production like equipment or environmental fluctuations can result in significant behavioral changes of the cells to produce changes in proteins. Thus, any change in any part of the process, or any of the raw materials, is subject to very close review and oversight by the FDA.

Most biologic manufacturers have had to make changes to their manufacturing systems at some point – such as changing the supplier of or replacing a piece of equipment. Also, for many successful biologics, the opening of a new facility to expand manufacturing capacity in order to treat more patients can be essential, and is a substantial undertaking. Also, sometimes manufacturers create a new master cell line and other more significant changes to a currently licensed product otherwise produced in the same facility. All these changes are always at the manufacturer’s discretion, but always under the oversight of the FDA in evaluating the use of comparability in support of manufacturing changes.¹⁴ Comparability ensures that the quality, safety and efficacy of all biologics are maintained pre- and post-manufacturing changes, and that patient access to biologics continues uninterrupted to the best extent possible. It also allows manufacturers to make manufacturing changes without having duplicate manufacturing facilities running concurrently.

What Are Biosimilars?

With the increasing use of biologics in treatment, as well as the upcoming expiration of patents for key “brand-name” biologics, plus increasing attention on the costs of health care, creating competition in the biologic marketplace may reduce the cost of these increasingly important medicines. Multiple stakeholders worked together to give FDA the authority to approve “generic” versions of biologics to provide competing and likely lower cost alternatives to the original brand name biologics without the need to impose price controls. These products have been successfully in use in other highly regulated countries and have increased access to more affordable care with no unusual or unexpected adverse outcomes for patients.

In the U.S. these competing products are biosimilars, and as described below, while their development time will likely be shorter, their quality must meet all the same standards of any originator biologic product. A biosimilar is a biologic product designed to be “highly similar”^{15,16} to a biologic product already approved by FDA, making them, in essence, “generic” versions of the original. Given the variation even within a single batch of some biologics, not all biosimilars will be exact copies of the biologic they reference, and are therefore not true “generics” in the manner of small molecule drugs.

As we will discuss further under the Policy Considerations section, there is now an established regulatory and approval framework, and biopharmaceutical companies are meeting with the FDA to prepare for product applications. As of the end of 2012, FDA has received 50 requests for initial meetings with potential biosimilars manufacturers to discuss development plans, have conducted 34 of those meetings, and received 12 biosimilar investigational new drug

¹⁴ ICH Q5E Guideline .Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (Nov. 2004), available at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf

¹⁵ The statutory terms used in Biologic Price Control and Innovation Act (BPCIA) portion of the ACA for the analytics only, “highly similar” is not applicable to the preclinical or clinical studies. Discussed later under FDA issues.

¹⁶ In Biologics Price Competition and Innovation Act (BPCIA)it is stated that the biosimilar must be demonstrated to be highly similar to the reference in terms of analytics, with preclinical and clinical studies in addition as determined to be necessary by the FDA

applications (IND), which allows product manufacturers to test a drug in humans.¹⁷ Manufacturers are interested in making biosimilars to 12 brand name therapies; FDA has not identified the specific targets, but this group likely includes medicines used by oncology patients. However, FDA has yet to receive an application for approval of a biosimilar. Biosimilars are already available in several other parts of the world, including places with regulatory standards similar to the U.S., like the European Union (EU) and Japan (collectively referred to as “highly regulated” markets).

While some other countries have allowed sales of biologic products by other manufacturers, and these are often less expensive than currently approved U.S. counterparts, many of these “alternative biologics” are not subject to the same oversight mandated in the U.S. and other highly regulated countries. As we will discuss below, the U.S. requires a much more substantial data package for a biosimilar than for a generic drug starting with comprehensive “fingerprinting” of the brand product as the reference for the biosimilar. The development of a biosimilar also requires head to head studies well beyond the basic analytic and pharmacokinetic studies necessary for generic drugs. These standards will not apply to the international “generic biologics” created independently, made to local standards, and lacking head-to-head comparisons to an originator biologic – however in those countries the alternative biologics may well serve an unmet medical need by even less well served patient populations.

In the U.S., biosimilars will rely on prior findings of their reference biologic product in the same manner as a generic drug relies on the prior finding of safety and efficacy of its reference brand drug today. The same FDA review divisions that approved the originator biologic will evaluate biosimilars, further assuring consistency in safety and efficacy standards for all biologics. Thus, the public can be confident that the FDA will apply the same standards to biosimilars as it applies to originator products, ensuring similar clinical outcomes for patients. These standards, however, will contribute to the costs of biosimilars, and as we will discuss further savings to same extent as from generic drugs are not expected immediately if ever.

Biosimilars Are Not Exact Copies of Originator Biologics

While it is true, as a scientific matter, that the biosimilar manufacturer will be unable to exactly reproduce the originator biologic when that biologic is a complex mixture, as noted above originator products vary over their lifetime too.¹⁸ In the vast majority of cases, these changes have proven acceptable, as the clinical outcomes of use of the products are indistinguishable. In rare instances, there have been problems with the use of comparability,¹⁹ but none to date with biosimilars approved in other highly regulated markets using this same approach.²⁰ What is most important is that consistent regulatory standards are applied by FDA to all biologics, irrespective of the manufacturers business model, and that state of the art science is applied to

¹⁷ Michael McCaughan and Derrick Gingery. Where are the Biosimilars? *The RPM Report*—December 14, 2012.

¹⁸ Schiestl M., Stangler T., Torella C., Cepeljnik T., Toll H., Grau R. Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals, *Nature Biotechnology*, Volume 29, Number 4, Pages 310-312 (April 2011).

¹⁹ Casadevall N. Immune-response and adverse reactions: PRCA case example.

http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500011064.pdf (accessed 4December 2012)

²⁰ Weise, M., Bielsky, MC., De Smet, K. et al. *Biosimilars: what clinicians should know*. *Blood*. October 2012.

ensure that all biologics made available to patients are safe and effective, and also products as efficiently and affordably as possible.

Although a biosimilar will be a copy of an existing biologic, made in a different cell line, with a different manufacturing and purification processes, in a different facility, it can be highly similar and generate the same clinical outcomes.²¹ Since the FDA applies the same scientific data standards equally to all biologics, a biosimilar will be as similar to the reference as the reference is to itself over its lifetime. Such consistency is essential to patient and provider confidence in biosimilars, as we have seen in Europe where there have been no reports of unexpected adverse events with any biosimilar on the market. Fortunately, indistinguishable clinical outcomes are possible as long as there is very careful analysis of the reference biologic through “reverse engineering,” and then head to head biosimilar product development to create a highly similar biologic product. The science now supports these approaches just as it has supported the development and manufacturing of biotechnology products over the past three decades.

Nonetheless, in order to prove that the biosimilar active ingredient, functional characteristics, and clinical characteristics are similar to the reference biologic, the FDA will likely require more extensive clinical testing before approving a biosimilar than they do when approving a manufacturing change. This will be the case even if the biosimilar is on the market in other highly regulated countries, and the cost of these additional studies will have to be acceptable to patients, payers and providers as we all become familiar with biosimilars in the US.

Finally, as we will discuss in the following section, unlike small molecule drugs, all biologics and therefore also all biosimilars have an inherent risk of immunogenicity—an unwanted immune response—that can be important for patients and providers to discuss thoroughly prior to the initiation of any biologic or biosimilar therapy.

There are Safety and Efficacy Concerns Inherent to Biologic Medicines

A particular safety concern with all biologics and biosimilars is the potential for the patient’s body to generate an unwanted immune response – much like with transplant rejection. This is due partially to the large size of biologics and biosimilars, and the immune system can readily recognize any protein different from a naturally occurring molecule. In contrast, this phenomenon of “immunogenicity” usually does not occur with small molecule drugs because they are so small that they go virtually undetected by the human immune system. If the patient’s body recognizes the biologic medicine as “foreign,” his/her own immune system starts creating its own antibodies to fight off this foreign-invader and eliminate the substance, just as the body would do with any foreign virus like the flu. In the example of a vaccine, this immune response is actually the desired outcome, as it helps prepare the system for subsequent exposure to the virus so that it may rapidly respond to the infectious agent.

²¹ Michał Nowicki, *Basic Facts about Biosimilars*, 30 *Kidney & Blood Pressure. Res.* 267, 268 (2007).

On the other hand, if the body attacks a medicine like insulin and creates an immune response, the subsequent administration of the drug may make the drug ineffective, and in the worst cases, induce an acute immunological response—called anaphylactic shock, which can be fatal. Additionally, the timing of an immune response to a biologic product may vary greatly. Some immune reactions occur right away after receiving the therapy, in which case the cause of the reaction is clear. However, an immune response to a biologic product may take time (several weeks or months) to become physically evident, in which case it may be difficult to determine whether it is a direct response to the biologic or simply a progression of the patient's disease.

Furthermore, if a patient receives exposure to multiple different biologic products over the course of their disease, it may be difficult to know which biologic caused the reaction. In extreme cases, instead of receiving additional amounts of a protein that they need, the patient may lose an essential substance needed by the body for the long term, even after discontinuing treatment. This was the case in Europe where a manufacturing change to Eprex[®] (epoetin alfa), given to increase red blood cells in the blood, led to rare instances of Pure Red Cell Aplasia, which is a type of autoimmune anemia.²² The patient's immune system destroyed the Eprex[®], and the antibodies cross-reacted and neutralized the patient's own erythropoietin (a substance normally produced by the body to create red blood cells). As a result, the patients became severely anemic—a result of low red blood cell counts, which can lead to extreme fatigue and undue strain on the heart; and some died. Subsequent studies showed that the Eprex[®] manufacturing change, a significant formulation change to remove human serum albumin because of the assumed risk of mad cow disease, resulted in aggregation of the active ingredient, leading to greater immunogenicity. Since this event, all biologics have undergone careful examination for evidence of aggregation using analytical methods (not clinical studies). In the U.S., the formulations for epoetin alfa (Epogen[®], Procrit[®]) have never changed.

While many immunological responses are not relevant, a few can be severe and occasionally some can be life threatening, requiring a high level of monitoring and testing throughout treatment with any biologic. However, there is no greater risk of a biosimilar being immunogenic than the originator biologic, and indeed the originator biologic can give the biosimilar manufacturer a very good indication as to what to look for during development. Furthermore, extensive pre-approval testing required by the FDA ensures an acceptable side effect level and sufficient efficacy when the final product reaches the marketplace. Finally, post-approval monitoring helps monitor any immunogenicity issues that may arise, even if infrequent. The European experience has shown that with the application of such high regulatory requirements there have been no unusual or unexpected adverse events with biosimilars compared to their originator counterparts.

²² Casadevall N. Immune-response and adverse reactions: PRCA case example. http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500011064.pdf (accessed 4December 2012)

Marketplace and Cost Considerations Creating Demand for Biosimilars

Biologics are important in oncology, with 6 of the 10 highest-selling biologics in the U.S. used in cancer treatment; however, the current cost of biologics can be very high.²³ Many stakeholders expect biosimilars to create more treatment options for patients, using more cost-effective manufacturing methods to create competition that will make biologics more affordable and expand patient access.²⁴ Nonetheless, due to the complexity of their production and development, biosimilars will likely not achieve the price differential seen among generic drugs in relation to their brand-name counterpart, or at least not in the near future.

The differences between traditional small molecule drugs and biologics have important implications. When patents and exclusivity for small-molecule drugs expire, generic versions of the drugs rapidly take a substantial share of the originator drug market and at substantially reduced price because it is relatively easy to make copies that contain the identical active ingredient.²⁵ These generics contain the same active ingredient as the branded reference product and compete purely on price. Doctors usually do not receive any active marketing information ("detailing") on these medicines since FDA has determined that they are fully substitutable – namely the pharmacist can switch the generic for the brand without consulting the original prescriber. The retail pharmacy dispenses most generic drugs, and while the doctor can check the "dispense as written" or "do not substitute" box on the prescription they write, s/he rarely does so as this will usually results in a larger cost-sharing burden for the patient. Generics are now a generally accepted component of a cost effective market place, and payers look to them to balance the availability of newer more expensive medicines as and when they become available. For patients with severe and life threatening diseases, the contribution by generics to encourage innovation and new medicines, as well as the savings for older ones is an essential component of care, but one that has historically in the US only applied to drugs and not biologics.

Biosimilar cost may remain seemingly high because the development of any biologic is more expensive than development of small molecule drugs. This is due to higher up-front fixed development costs and facility costs.²⁶ Indeed, the initial development of a biosimilar product may even have a higher cost than an originator biologic, due to the need to purchase the reference product, and to establish high similarity analytically. This will be essential for any biosimilar, even as the savings during the clinical trial stages of development remain uncertain - although most are assuming that clinical development costs for a biosimilar will be substantially less than those for an originator biologic. The amount of investment saved for a biosimilar versus an originator biologic will likely hinge on the amount of clinical testing needed for approval; this will likely vary from biosimilar to biosimilar, but the biggest factor may be the

²³ Hirsch, B., and Lyman, G. *Are Biosimilars Ready for Primetime in the United States?* *J Natl Compr Canc Netw* 2011;9:934-942.

²⁴ McCamish, Mark. *The Clinical and Financial Impact of Biosimilars*. Health Reform 2012. Available at http://www.cdmihealth.com/CDMI_Journal/Fall_2012/index.html#/40/zoomed. Last accessed November 9, 2012.

²⁵ GPhA. *Generic Drug Savings in the U.S. (Fourth Annual Addition: 2012)*. <http://www.gphaonline.org/sites/default/files/IMS%20Study%20Aug%202012%20WEB.pdf>.

²⁶ Hirsch, B., and Lyman, G. *Are Biosimilars Ready for Primetime in the United States?* *J Natl Compr Canc Netw* 2011;9:934-942.

extrapolation between indications allowed for the biosimilar without individual clinical studies for each. These factors are further discussed later in the primer.

In Europe, the savings for the same biosimilar in different countries has varied enormously depending on the details of the purchasing system. Nonetheless, a 25 percent discount on a high-cost medication can be valuable, and the competition created once biosimilars enter the market may bring down costs for the innovator products as well.²⁷ This was the case in Europe, in particular in Germany when the biosimilar ESAs first became available. Highly regulated markets such as Europe currently account for over 80% of biosimilar spending, but the market share within individual countries is extremely variable.²⁸

When biosimilar products first reach the U.S. market, the expected immediate cost reduction is 25-30 percent less than originator biologics, but this estimate is a tentative approximation at best.²⁹ This is because one of the biggest unknowns affecting a biosimilar's price is the cost to initiate and support the product development process, and the market factors they will face after launch. Small-molecule generics can cost 75-90 percent lower than branded products because payers typically require their use, pharmacies automatically fill generics, and manufacturers have little overhead in terms of marketing, patient services and physician support. However, the same is not true for biosimilar products.

The ultimate determining factor of a biosimilar's price will depend on the nature and extent of any costly clinical studies required by the FDA to gain market access and market share. The resources necessary to conduct adequate clinical studies for product approval may erode projected biosimilar cost savings. Additionally, as biosimilar complexity increases, so will the costs related to its clinical trials. Such studies will apply even for those products already on the market in Europe, and even after approval, it is not clear how payers will respond. Finally, since the manufacturing costs of biologic products are substantially higher for small molecule drugs, and their respective generics, this in turn will keep the price of biologics relatively high in comparison to generic small molecule drugs. Most stakeholders expect biosimilars to require detailing to prescribers in the manner of originator products – they will not compete like regular generics namely on price.

²⁷ Hirsch, B., and Lyman, G. *Are Biosimilars Ready for Primetime in the United States?* *J Natl Compr Canc Netw* 2011;9:934-942.

²⁸ IMS Health. *The Global Use of Medicines: Outlook Through 2015*. Available at http://www.imshealth.com/imshealth/Global/Content/IMS%20Institute/Documents/Global_Use_of_Medicines_Report1.pdf. Last accessed November 8, 2012.

²⁹ IMS Institute for Healthcare Informatics. *The Global Use of Medicines: Outlook Through 2015*. (May 2011), available at http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Global_Use_of_Medicines_Report.pdf

Figure 5: Ultimate Patient Savings and Access for Biosimilars Will Depend on Several Regulatory and Reimbursement Factors



Since the introduction of the European biosimilars approval pathway in 2004, several biosimilars have launched – a total of 14 biosimilar products are on the market today (see Figure 6 below). These products are at the smaller size range of biologic molecules (see Figure 1 above). The European Medicines Agency (EMA, the European counterpart to the FDA) is already reviewing the first mAb biosimilar application (rumored to reference rituximab, used in the treatment of leukemias and lymphomas).³⁰ Meanwhile, a biosimilar to Remicade[®] (infliximab), called Remsima[®], has received approval in South Korea. Biosimilar uptake in the European market was slower than expected initially, but utilization has increased alongside greater familiarity and growing trust in the products available.³¹ For instance in Sweden, biosimilars to filgrastim now predominate in the market, exceeding by volume that of the reference product, Neupogen[®] (filgrastim).

With the introduction of the new FDA biosimilars approval pathway, when patent protections and exclusivity protections of originator biologics end (12 years for biologics versus 5 years for small molecule drugs), opportunities for competition in the biologics market is being created. Companies can now create biosimilar products and have them approved by FDA for the same indications as the brand reference product. To receive a biosimilar designation, these medicines will go through functional (preclinical) and clinical studies as well as head-to-head trials with the originator reference product. Manufacturers can either pursue a "biosimilar" label for these products or, if they provide additional data to FDA, they may obtain an "interchangeable biosimilar" designation which means that FDA has agreed that the biosimilars is substitutable for its reference without the involvement of the original prescriber.

³⁰ Weise, M., Bielsky, MC., De Smet, K. et al. *Biosimilars: what clinicians should know*. Blood. October 2012

³¹ Minhetti, P., Rocco, P., Cilirzo, F. et al. The regulatory framework of biosimilars in the European Union. *Drug Discovery Today*. 2012; 17(1-2):63-70.

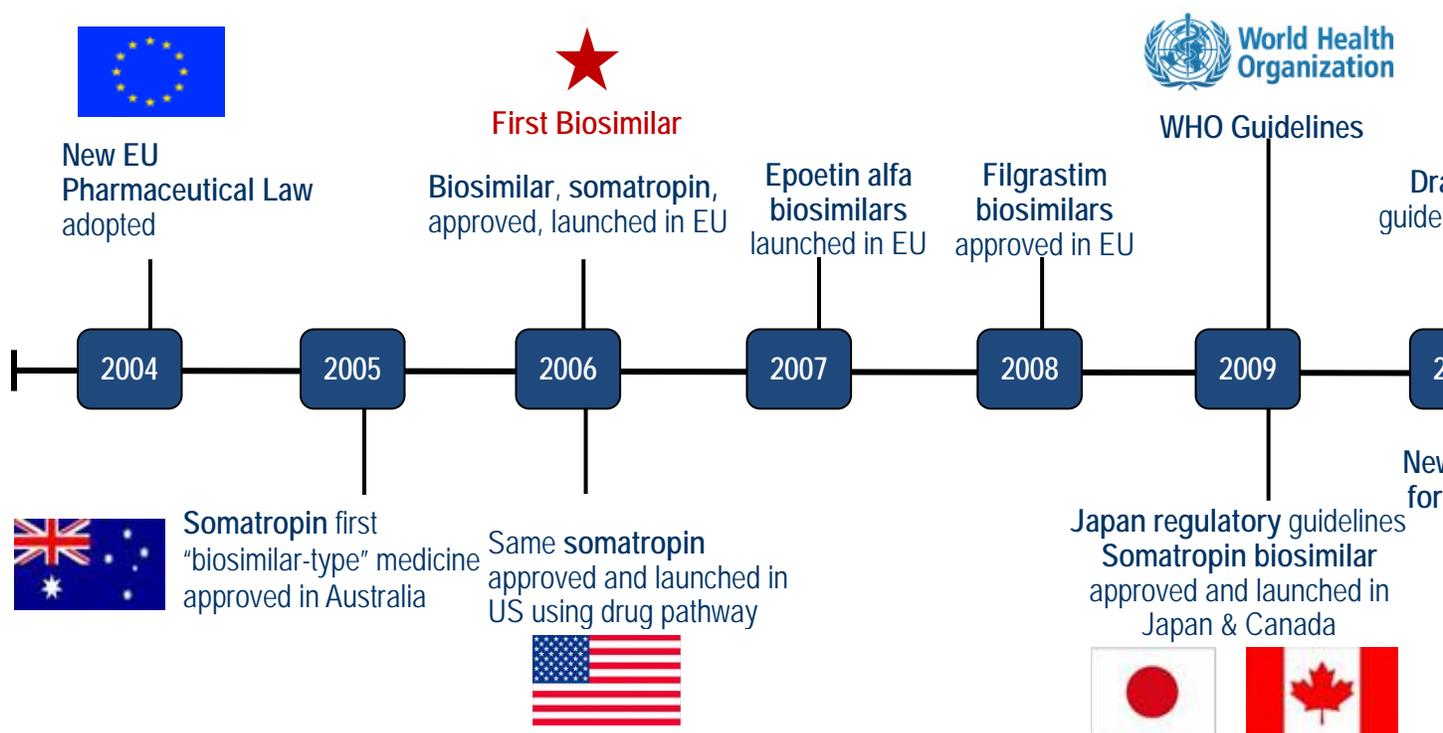
Policy Considerations for Biosimilars: Emerging Stakeholder Issues

While the Patient Protection Affordable Care Act (ACA) establishes the overall framework for FDA approval and certain Medicare payment for biosimilars, there are several policy and practical steps that regulators, payers, states, and other stakeholders must take before patients will have access to biosimilar treatment options. In this section we will outline the "knowns" and the "unknowns" along that access continuum, and the current state of play regarding each of the "unknowns."

In particular, many unknowns still exist regarding how the FDA will evaluate biosimilar product applications. In the first part of this section, we will discuss the status of FDA implementation of the biosimilar approval pathway, separated into the issues that will affect the science of FDA approval and the additional issues that will affect the timeliness and cost of patient access to these therapies. Second, we will address the key issues payers (private and Medicare) will face in determining access to biosimilars to their members/beneficiaries. Finally, states will play a significant role in determining access to biosimilars, to the extent they allow pharmacists to counsel or require them to substitute biosimilars for those biologics dispensed at the pharmacy. In exploring the role of each of these stakeholders in determining the timeliness and cost of biosimilars to patients, as well as their actions to-date, the following section explores potential opportunities for educating these stakeholders—as well as physicians and fellow patients—on the key issues that will affect ultimate patient access and affordability.

The U.S. continues to lag other countries on the biosimilars front, only recently enacting a biosimilar approval pathway, and not yet having any products approved via this pathway to date (Figure 6). It is important to note, and we will further discuss later, that the U.S. is unique in that the FDA can grant interchangeability status to biosimilars – no other country has this regulatory authority, and most of their statutes are silent on the issue of interchangeability. Biosimilars neither are, nor are they not, interchangeable with that of their reference branded product.

Figure 6: Several Countries Have Pursued Biosimilar Regulation and Approval



FDA Has an Established Process to Regulate Biologic Therapies

Product manufacturers design, develop, and extensively evaluate all new biologics when they are interested in bringing a new medicine to the U.S. market for patient use. These candidates are initially analyzed and tested in test tubes using functional tests, then in animals (preclinical testing), and only when everything looks good are they tested in humans – first in small studies in healthy volunteers, then ultimately for efficacy in patients with the desired condition. These tests show how the body absorbs, uses, and eliminate a drug from the system.

If preclinical studies do not raise any concerns, manufacturers seek permission from FDA to conduct investigational studies in humans.³² There are very tight controls of all stages of testing in humans, requiring careful monitoring and informing patients of the risks of participation. Information on cancer studies underway is available to the public, to encourage volunteers for these trials, and in order to get data on safety and efficacy as quickly as possible.³³

³² <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ParticipatinginClinicalTrials/ucm129557.htm>
³³ From <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ParticipatinginClinicalTrials/ucm129557.htm>

Clinical trials for drugs and biologics occur in three phases prior to product launch (plus additional post-market testing as needed), and these are required for nearly all originator biologic products.³⁴

- Phase 1 introduces the therapy into healthy volunteers in very low doses to determine safety and how the human body processes the drug.
- Phase 2 tests the medicine in small groups of people with the disease to study safety and dosing.
- Phase 3 tests the medicine in a larger population of people with the disease of concern, and looks at both safety and efficacy (does the medicine work?). The FDA reviews this data and makes the ultimate decision to approve or not approve a product.
- Phase 4 (after approval and only as deemed necessary by FDA) Additional testing and monitoring after the product is approved and launches, is determined as part of the approval process; these post-marketing studies monitor safety and therapy over time.

FDA Is Establishing Its Pathway to Regulate Biosimilar Products³⁵

FDA received formal authority to approve biologics that refer to a previously approved biologic product, in the manner of generic drugs, in 2010. The passage of the Biologics Price Competition and Innovation Act (BPCIA) within the ACA created a formal new regulatory pathway—351(k) pathway—for the FDA approval of biosimilars.^{36,37} It is up to the FDA how they implement this new authority, and they alone get to determine the nature and the extent of the studies, analytical, functional and clinical studies that they believe necessary to establish biosimilarity. All biologics, whether originator or biosimilar, have to achieve the same standards of safety, purity and potency. As such FDA regulates biosimilars to the same standard as any other biologic.

FDA has faced a challenge in implementing the biosimilar pathway, as some reference products may have received approval decades ago under local standards, and it may not be exactly the same product that is available in each locale. Thus, a reference product available in Europe for an EU biosimilar may not be exactly the same as the U.S. reference product that would be needed for a U.S. biosimilar. For example, formulations vary as was discussed above for the ESAs.³⁸ However, without global development, clinical studies will need to be repeated and this will affect the cost for patients. Also the different regulatory requirements combined with the economics that pertain to the various healthcare systems mean that biosimilars approved in one

³⁴ Full clinical trials are not required when not feasible, such as for the annual flu vaccine

³⁵ FDA Information for Consumers (Biosimilars)

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm>

³⁶ U.S. Congress. House. Biologics Price Competition and Innovation Act of 2009 of the Patient Protection and Affordable Care Act. (Public Law No. 111-148).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf>

³⁷ Patient Protection and Affordable Care Act, Pub. L. No: 111-148:804

³⁸ There is no HSA free epoetin product in the US as the manufacturing change in Europe that precipitated the PRCA problem was never implemented in the US. Hence, even though the active ingredient in European Epoetin alfa products is the same in the EU and US, the final drug products are not the same. Hence it is not clear that a biosimilar to the European version will also be considered biosimilar to the US version.

country may not be biosimilars in another. We already have multiple instances of this in EU and US.³⁹

Nonetheless, FDA has extensive experience with originator biologics, especially recombinant products, and continues to lead the world in making these products available to patients and their healthcare providers. These products will provide the reference products for all the biosimilars in the U.S. Unlike with small molecule generics, more data is necessary upfront in the development process and these are the decisions that potential biosimilar manufacturers need to make today. As discussed above, this additional early data requirement translates into greater up-front costs as well as the potential to have to repeat studies if they do not initially gather the correct data. Anything that means more time and investment for manufacturers can mean greater costs for patients.

FDA has begun implementation of their new authorities. The agency has held two public meetings, in Fall 2010 and Spring 2012, published three draft guidance documents for comment, and is holding multiple private meetings with manufacturers to discuss development plans for individual products. The FDA is familiar and fully equipped with the scientific expertise and experience needed to approve biosimilars, just as they are for originator biologics, but there is still a great deal of uncertainty remaining regarding how the FDA will implement the biosimilarity regulatory legislation and great concern that an excess of conservatism will make the savings for patients nominal at best. What is certain is that all biosimilar products will be required to meet the same standards of safety, purity and potency as originator biologics, irrespective of whether the FDA ever feels ready to designate them as interchangeable with their reference product.

In the remainder of this section, we will explore three specific components of the pathway FDA is implementing—determining biosimilarity, criteria for extrapolating additional indications on an FDA label, and designation of interchangeability. How FDA moves forward on each of these issues will determine the timeliness and cost of the product to patients (based on the studies required to get approval), as well as how providers and payers perceive the written label for the product.

FDA Is Establishing Criteria for Manufacturers to Demonstrate Biosimilarity

Under the BPCIA definition of biosimilarity, manufacturers must demonstrate that their biosimilar candidate is highly similar to their chosen FDA-approved reference product using state of the art analytical tests in head-to-head studies (minor differences may be acceptable and even expected, in clinically inactive components), and that as a result there are no clinically meaningful differences expected for patients treated with the biosimilar or the originator biologic.⁴⁰ Some fear that the initial analytical study requirements to establish a highly similar product may discourage some potential manufacturers, since the upfront investments will be

³⁹ Somatropin, filgrastim, enoxaparin all provide examples of this

⁴⁰ Patient Protection and Affordable Care Act. Sections 7001-7003. Available at <http://housedocs.house.gov/energycommerce/ppacacon.pdf>. Accessed November 9, 2012

large. The manufacturer must analyze the reference to create the “goalposts” between which the biosimilar must fit.⁴¹

Prospective biosimilar manufacturers must share this analytical evidence of “high similarity” with the FDA, who will then negotiate the nature and extent of the preclinical and clinical studies expected to confirm biosimilarity. If the manufacturer can make their biosimilar candidate indistinguishable to the reference product,⁴² they can expect to conduct fewer animal and clinical studies. However, unlike the current approach to manufacturing changes, FDA will likely require clinical studies to confirm biosimilarity. The law is very clear that FDA can waive any analytical, functional or clinical studies that they consider to be unnecessary to establish biosimilarity, but beyond a potential waiver for Phase 2 studies it is not clear what, if any steps, will be deemed unnecessary. This does create a quandary for FDA, as they do not want to require unnecessary studies either, as this could delay access and increase cost.

FDA Will Determine When Biosimilars Can “Extrapolate” Additional Indications

The next question for FDA is how many indications of the originator reference product will appear on the label of the biosimilar. For instance, the biosimilar manufacturer must show that the mechanism of action (the way the medicine works to produce the desired clinical outcome) of each of the indications to which they want to extrapolate is the same as that for the indication on which they have conducted their demonstration of biosimilarity. Further, for the biosimilar, the route of administration (the way the medicine is given), the dosage form or physical form of the dose, and strength of the medicine (amount of medicine in a given volume) should all be the same as that of the reference product.

How the FDA moves forward with extrapolation is important because the time and effort to achieve multiple indications can factor into the ultimate price of the product to the patient. In addition, the labeled indications often link to the conditions for which payers are willing to reimburse for use of the product.

An FDA Interchangeability Designation has Implications for Substitution

When developing a biosimilar, manufacturers can either pursue a “biosimilar” label or, if they provide additional data to FDA, they may obtain an “interchangeable biosimilar” designation which means that FDA has agreed that the biosimilar is substitutable for its reference without the involvement of the original prescriber. An interchangeable biosimilar should produce the same clinical results as the brand biologic and switching between the brand and the biosimilar is safe and effective for patients. In the case of generic small molecule drugs, the generic always has all the indications and is fully interchangeable with the reference product.⁴³ The generic has the identical label to the reference originator product – absent the brand name. Within the class

⁴¹ McCamish M. and Woollett G., an invited article on “The State of the Art in the Development of Biosimilars”, *Clinical Pharmacology and Therapeutics*, Nature’s Clinical Pharmacology & Therapeutics, Regulatory Issue, March 2012. Available at: <http://www.nature.com/clpt/journal/v91/n3/full/clpt2011343a.html>.

⁴² McCamish M. and Woollett G. “Worldwide experience with biosimilar development”, *mAbs* (March/April 2011) 3:2, 209-217. Available at: <http://www.landesbioscience.com/journals/mabs/article/15005/>.

⁴³ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No 98-417, 98 Stat. 1585

of biologic therapies known as monoclonal antibodies), those therapies targeting oncology alone account for over 14 percent of the total U.S. spending on biologics.⁴⁴

The question is how FDA expects demonstration of interchangeability, how the FDA will word the labels for such products, and how the FDA designation will affect the practice of medicine/pharmacy for each state. The new federal law requires that the biosimilar manufacturer show that switching between the biosimilar and its reference does not create safety or efficacy concerns,⁴⁵ but the law does not require any specific studies, clinical or otherwise, and leaves the nature of the evidence required up to FDA. The FDA requirements for an interchangeability designation for a biosimilar, as well as the nature of the product labeling will affect the ability of current systems, such as state substitution laws (discussed further in a later section), to recognize biosimilars and allow rapid substitution of interchangeable products.

As a formal legal matter, a manufacturer does not need to get a biosimilar approved and then undertake a second step to seek interchangeability and could therefore submit such an application for an interchangeable biosimilar today. However, that may risk a delay to the approval of a biosimilar because the FDA has revealed little to-date about the data they will require to approve an interchangeable biosimilar. The FDA has acknowledged that a manufacturer can indeed file in a single step for approval of an interchangeable biosimilar; however they see this as being a difficult proposition at this time.

The concept of interchangeability is not a global concept as no other regulator besides FDA has explicit authority to designate a biosimilar as interchangeable with its reference. No approved biosimilars to-date in Europe and other markets have an interchangeable designation, but in practice, countries have switched patients between biosimilars and biologics without this designation. For example, Poland has switched their short stature patients between different somatropins a number of times, and this means individual patients have received different versions of the therapy during their course of treatment. No unusual or unexpected issues have appeared for any marketed biosimilar when compared to their reference product, but few studies have appeared in the scientific, peer reviewed literature to date. Similarly, no data has been published suggesting that switching patients between different originator biologics for the same conditions, such as different ESAs, creates a safety problem, but in the absence of organized studies, conclusions are tenuous.

In the U.S. there are implications for each and every one of these decisions about biosimilars and interchangeable biosimilars for providers and patients. For self-administered drugs, substitution of an interchangeable biosimilar will likely take place at the pharmacy for a brand name product, depending on state substitution laws.⁴⁶ For products administered by a physician, such as an intravenous infusion, the physician may choose whether or not to

⁴⁴ IMS Health. Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape. Available at http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_Whitepaper.pdf. Last accessed November 8, 2012.

⁴⁵ http://www.clinicaloncology.com/ViewArticle.aspx?d=Policy+and+Management&d_id=151&i=May+2012&i_id=842&a_id=20877

⁴⁶ Some state laws but not others could accommodate biosimilars today by treating interchangeable biosimilars in the same manner as generic drugs. However the expectation is that many state laws will be rewritten as biosimilars start to be approved by FDA and more becomes understood as to how they can and should be being used. Cost will be a significant consideration for state legislators

administer the biosimilar product in place of the originator quite independently of an FDA designation of interchangeability. As with generic drugs, the FDA's designation of interchangeability is a scientific and regulatory one, and the individual states then have the responsibility to decide how that designation is recognized in both the practice of pharmacy, and the practice of medicine.^{47,48}

FDA Will Affect Access to Biosimilars, Beyond Scientific Pathway Considerations

Manufacturers face multiple unknowns with the FDA implementation of the new regulatory pathway for biosimilars—including the conditions for biosimilarity, extrapolation, and interchangeability noted above—and this is likely part of the reason that no biosimilars are under review, despite their increasing success in Europe and other markets.

Beyond the scientific considerations discussed in the previous section, however, there are other ways in which FDA will affect access to biosimilars. First, FDA is implementing new legislation to fund their work in approving biosimilars; however this law contains several milestones that will be critical to timely access. Second, as stakeholders debate the potential need to trace any adverse effects from biologics and biosimilars, as noted above, the FDA label and product name have arisen as a potential solution that will likely be under debate in the coming year. We discuss these two issues in further detail below.

Biosimilar Manufacturers Will Need to Pay User Fees During Development

In parallel to BPCIA, another statute, the Biosimilar User Fee Act of 2012 (BsUFA) designated the amount that biosimilar manufacturers must pay FDA to review their applications. User fees give FDA the resources to implement the new pathway by the Agency being able to hold meetings with potential biosimilar manufacturers, and to review applications when submitted. FDA can accept an application for a biosimilar four years after the Agency approved the reference originator product, but cannot approve it until 12 years after approval of the originator—known as “exclusivity.” It means that for any biologic, there will never be a biosimilar available within 12 years of the approval date. This is quite separate from patents, which could extend beyond 12 years, but in most cases would not go beyond the 14 allowed for all medicines under the patent provisions of the Hatch-Waxman Act that created generic drugs.

Biosimilar manufacturers will pay a user fee to FDA to review their application and discuss product development plans at meetings. Importantly, a portion of the biosimilar fees are due as soon as the biosimilar manufacturer asks for their first meeting with FDA. Such fees are not required for pre-filing meetings for originator products, and if a manufacturer elects to have meetings with the FDA for a standalone application they will not need to pay. The rationale is that these partial fees represent start-up costs for getting the biosimilar pathway up and running. However, if a biosimilar manufacturer does not pay their fee on time, FDA can put the biosimilar

⁴⁷ U.S. Food and Drug Administration, Orange Book Preface. 30th Ed. Washington, DC.: U.S. Food and Drug Administration.

⁴⁸ http://primaryimmune.org/advocacy_center/pdfs/health_care_reform/Biosimilars_Congressional_Research_Service_Report.pdf

development program on financial hold (equivalent to clinical hold), and this prevents the manufacturer from pursuing the studies that they need to get the data necessary for registration.

Naming of Biosimilars Coming Under Increasing Scrutiny in the Debate of Patient Safety

Naming is not an issue that appears in BPCIA, but it has come under debate as a possible solution to prospective safety concerns for biosimilars. Biosimilars to date in other countries have had a brand or trade name, as well as a nonproprietary or generic name. The FDA position, submitted to the World Health Organization (WHO) in 2006 supported the international nonproprietary name (INN) system administered by WHO, to advise healthcare providers with a single name for the active ingredient in medicines.⁴⁹ In Europe, and elsewhere, the majority of biosimilars share the INN of their reference product. Currently, the INN is simply the name for the active ingredient in a medicine, and the WHO system aims to coordinate this world wide such that prescribers have a ready way of knowing what the active ingredient is in any medicine. Different products that share INNs have rarely been compared in the past, and are not therapeutically equivalent through sharing the INN. Indeed the INN does not contain information on dose, concentration, formulation or multiple other attributes of the product that are critically important to appropriate use by patients.

Having different INNs, also called United States Adopted Name (USAN) in the U.S., has significant ramifications for how biosimilars are used. For instance, most states require substitutable drugs to share INNs, and it is likely that different generic names would slow utilization of biosimilars. Many stakeholders are concerned that different names could also lead to patient and prescriber confusion, affect safety, and negatively affect interchangeability, thereby reducing patient access.

Advocates for unique naming for biosimilars feel that using a shared INN between an originator biologic and its subsequent biosimilar could lead to patients unaware of what drug they are receiving, therefore making it a challenge to attribute adverse outcomes to a particular product. On the other hand, proponents for shared INNs project a potential for overdosing and mis-dosing medicines if different INNs exist for the originator biologic and its subsequent biosimilars, as a patient could inadvertently receive prescriptions for two versions of the same biologic product.

FDA officials have stated that further guidance on biosimilar naming may be forthcoming in 2013, but in the interim the regulatory and market uncertainty have caused stakeholders to promote positions via various channels. Nonetheless, despite many opinions on the naming issue, there is agreement on a need for synchronization with international regulations in order to accurately track adverse events after product approval. The recording of complete information for every patient is essential for all medicines, and no system can compensate for the failure of medical providers to keep complete records.

⁴⁹ U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars September 1, 2006

Payer Reimbursement for Biologics and Biosimilars Will Affect Patient Access

How the costs of a biologic are covered and paid, and how much the treatment costs a patient is largely driven by two factors – the type of insurance a patient has and the setting in which the product is administered. A physician or other health care professional in a medical office or hospital setting administers many oncology treatments, particularly those medicines that require administration by intravenous (IV) infusions. These types of products typically receive coverage under an insurance plan's medical benefit. By contrast, self-administered treatments, such as pills or self-injectable products usually receive coverage under insurers' pharmacy benefits.

The current influence of physicians, health plans, and pharmacists over what specific product a patient receives varies significantly between the medical and pharmacy benefits, and will continue to be important when biosimilar treatments are approved by the FDA and available to patients. In the appendix we describe in detail the ways in which Medicare and private insurers cover and pay for drugs and biologics currently, and how they are likely to cover and pay for biosimilars, as well as how insurers' policies directly determine patients' out-of-pocket costs for their medications (see Appendix).

U.S. States May Have Additional Authority in Determining Access to Biosimilars

States will have two very important roles in determining how its constituents use biosimilar products. The first role relates to a pharmacist substituting a biosimilar for a prescribed originator biologic without physician consent.⁵⁰ Traditionally, the states define who has the authority to specifically decide what medicine a patient receives, and states vary regarding pharmacist discretion to substitute small molecule drugs without physician consent. However, since these current laws intended to apply to generic small molecule drugs, it is not clear how states will apply this to biologics and biosimilar.

Stakeholders have expressed concern about states' automatic substitution policies that may apply to biosimilars, even when there is no federal determination of interchangeability. Therefore, without specific guidance from the FDA, state authorities may have to attempt to make decisions about the definition of interchangeability. Some believe that state substitution laws in all 50 states will require revisions to accommodate biosimilars, and their solutions may vary – for some an FDA designation of interchangeability may be sufficient, but others may require additional information beyond the FDA designation.

The second area in which states will have a role with regard to biosimilars is deciding which products are included on state formularies—lists of medicines that are part of the state-sponsored health coverage plans, such as Medicaid and Children's Health Insurance Program (CHIP). These state level decisions will ultimately affect local patient access.

⁵⁰ U.S. Food and Drug Administration, Orange Book, available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>

Potential Opportunities for Stakeholder Education

Experience and confidence in older products may influence provider management initially as was the case in the European market, and originator biologics may choose to compete on price as was the case in Germany with the ESAs. The availability of biologic products does not automatically translate into clinicians immediately using these products with comfort and confidence. For instance, devices used to administer biologics may vary, such as the syringes for injectable products, and this can be very important to patients and providers and their confidence in use of these products. Often patents apply to the devices, as well as the medicines themselves, and it may be these patents that become the most important to availability of acceptable biosimilars.

Education can play an important role in informing patients and providers about these variations, their implications, expected outcomes, and what it means for the safety of those utilizing the products. There is a need for patient and provider education about safety and efficacy issues surrounding all biologics, including biosimilars products, as well as ready access to all available information on any product differences, such as their associated devices, in order to avoid confusion and enable informed choices. Patients and prescribers have to feel comfortable with their options even as payers and regulators work out how to incentivize more efficient manufacturing and market place competition to enable access and affordability for all. Ultimately, the biologic or biosimilar manufacturer is typically responsible for providing this education across stakeholders, which can simultaneously increase product price while also ensuring patient access.

The keys to success for biosimilars are informing and educating patients and providers on: the benefits and safety challenges of reproducing biologic drugs; the naming and labeling system issues, and understanding that the FDA's approval of a biosimilar as a standalone product does not in and of itself mean that it is interchangeable with its originator branded biologic. Patient and provider education will be paramount for biosimilar acceptance and uptake by relevant stakeholders. While stakeholders such as providers and payers will review the science behind a biosimilar to make sure it performs as well as the originator branded biologic, the amount of evidence desired by each party may vary. Therefore education must inform stakeholders that a smaller data package (due to the use of extrapolation) does not equal any less rigor; but instead prevents waste of resources and redundancies. This is important because if stakeholders are not clear on this fact and feel that the science used in the biosimilar's development process is too "soft," stakeholders may position these products as second-line, administered only after an originator biologic product has failed rather than in place of the originator biologic. Health plans will also have to conduct scientific evaluations of biosimilars and then decide whether to include them on formularies—a list of medicine approved for prescribing under a particular payer reimbursement plan. Payer-mandated switching is unlikely to occur immediately, so the first biosimilars product approved in the U.S. may prove to be a learning experience. However, as more biosimilars come to market, and provider and consumer confidence increases in these products, biosimilars will be on the path to faster integration and uptake.

Conclusions

Biologics are essential for cancer treatment, both in addressing the underlying disease and in offering supportive care to patients undergoing treatment. The nature of biologics to date – single source, difficult and expensive to manufacture, as well as high initial development costs have led to these products being very high-priced. The advent of biosimilars – highly similar alternatives to originator biologics that offer the same therapeutic benefit – hold the promise of lower costs and expanding access for patients who rely on biologic medicines.

A number of factors remain undecided that will ultimately determine how soon, and at what price, biosimilars will be available to patients. FDA regulatory standards and data requirements for biosimilars and interchangeable biosimilars continue to evolve, and we may not attain full clarity in the immediate future, but it is clear that initial development costs will be significantly greater than for traditional generics. Manufacturers' approaches to developing biosimilar products and filing applications for approval with the FDA will continue to evolve accordingly, as industry navigates the scientific and business uncertainty around concepts such as biosimilarity, extrapolation, and interchangeability.

Once manufacturers receive regulatory approval, a number of factors will influence how they price biosimilars, including product development costs, the need for intensive patient support and other “value-add” services, and responses through competitive pricing by their reference product manufacturer, as well as, eventually, other biosimilar (or originator) competitors. The price of products will have a direct impact on patients' ability to afford these products, as the cost-sharing for biologics, and potentially for biosimilars, often is a percentage of total costs rather than a flat copayment.

Whether a product is physician administered or dispensed via the retail pharmacy may also affect whether a patient receives the originator product or biosimilar, particularly if automatic generic substitution laws are applicable to biosimilars or interchangeable biosimilars in many states (this is and will continue to be a current “hot topic” for many state legislatures in 2013). Physicians' prescribing habits will also drive or delay uptake of biosimilars, as will policies put in place by Medicare, private insurers, and state Medicaid programs that can expand or limit access to treatments.

The rapidity with which patients will have access to potentially lower-cost, biosimilar products will depend on these factors, but ultimately increasing competition in the biologics market is likely to increase patient access to these life-saving therapies as well as give greater confidence in the surety of supply of biologics overall.

Appendix

Medicare Coverage and Payment of Biologics, in Particular the Role of Part B and Part D

The Medicare program consists of four parts.

- Part A covers hospital inpatient services and some post-hospitalization care like rehabilitation in a skilled nursing facility and home health care for qualifying beneficiaries. All Medicare beneficiaries receive Part A coverage.
- Part B covers outpatient care, including physician services, hospital outpatient care, and most drugs and biologics delivered in these settings of care, including many oncology treatments. Medicare beneficiaries receive Part B coverage unless they opt-out. As a result, the vast majority of Medicare patients have Part B coverage.
- Part C refers to Medicare Advantage plans, or Medicare insurance managed through private insurers, typically covering the hospitalizations, outpatient services, and prescription drug coverage. Part C is a voluntary option for Medicare beneficiaries who can choose to enroll in a Medicare Advantage plan in lieu of traditional Medicare fee-for-service (Parts A and B described above).
- Part D is the outpatient prescription drug benefit, covering self-administered drugs and biologics typically purchased through the retail pharmacy. Part D is optional for Medicare beneficiaries and they must actively seek out and enroll in a plan. In 2012, approximately [60%] of Medicare patients chose to enroll in a Part D plan.

Medicare Part B Coverage

Under Part B, Medicare covers FDA-approved drugs and biologics administered by a physician. With minimal exceptions, Medicare covers Part B drugs for their FDA-labeled indications, giving patients access to whatever treatments their physicians choose to deliver. For cancer treatment, Medicare also extends coverage of Part B drugs to “off-label” uses. Through this policy, Medicare covers and pays for oncology treatments supported by medical research and publications, even if the exact indication is not on the FDA label. For example, Medicare covers Rituxan[®] (rituximab) for a variety of cancer-types⁵¹, although its only FDA-approved oncology indications are for Non-Hodgkin’s Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL). The case must still be made for coverage and payment, but the mechanisms are in place for this to happen. While it is unclear whether or not Medicare will place any coverage restrictions on biosimilars, the precedent for coverage under Part B being to allow oncology physicians, uniquely, a great deal of leeway in what products they use for cancer treatment will likely be extended to biosimilars too. Given this, Medicare coverage for biosimilar products will likely

⁵¹ Off-label uses of Rituxan covered by Medicare include second-line or salvage therapy with or without radiation therapy (RT) prior to autologous stem cell rescue for progressive disease or for relapsed disease in patients initially treated with chemotherapy with or without RT in combination with bendamustine; low grade or follicular CD20-positive, B-cell non-Hodgkin’s lymphomas (re-induction treatment appropriate for responders and patients with stable disease); and intermediate and high grade NHL when used as a single agent, in combination with a CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) chemotherapy regimen, or in combination with other agents active in the disease.

mirror the coverage of their reference products, including coverage of off-label indications; however this is not yet certain.

Medicare Part B Payment

The Social Security Act sets payment rates for Medicare Part B drugs and biologics in law. Drugs and biologics delivered “incident to” a physician’s services, such as IV oncolytics, receive payment under a “buy and bill” system. Under this system, physicians (or hospital outpatient departments) keep an inventory of treatments which they have purchased to treat their patients. After administering a drug they’ve purchased to a Medicare patient, the physician bills Medicare for the drug or biologic, along with a charge for their services related to delivering the treatment.

Medicare pays physicians for Part B drugs and biologics based on an established payment metric known as “average sales price” or ASP. Each quarter, drug and biologic manufacturers report their sales to Medicare, including the number of units sold and the price of each unit, inclusive of all discounts. Medicare uses this data to calculate each product’s ASP and in turn pays physicians who buy and bill for those products at 106% of ASP. Congress set the payment amount six percent above the calculated ASP to ensure full reimbursement to the majority of physicians for the drugs they purchase and administer, with many receiving slightly more than their purchase price in order to help offset the overhead associated with keeping an inventory of Part B drugs on hand.

Single-source products each have their own unique ASP. Currently, all biologics on the market are single-source products. Multi-source drugs, or those brands with generic versions on the market, receive payment based on a volume-weighted ASP which blends the market prices for all versions of a product available. Typically, once generic competition launches for a branded small molecule drug, the ASP decreases, as cheaper generic versions take up market share and drive the overall, volume-weighted price down. This is because generic drugs typically cost a fraction of the price of originator small molecule products.

As discussed earlier, biosimilars are not “generic” versions of originator biologics in the same way generic drugs are copies of small molecule originator drugs, so the established methodology for shared ASPs does not apply to biosimilars. In the Affordable Care Act, Congress included payment provisions for biosimilars to ensure that Part B drug payment would represent an even playing field for innovator biologics and biosimilar competitors. Since Part B biologics receive payment at 106% of their ASP, the more expensive a product is, the larger the 6% mark-up is. If a physician had the choice between an originator biologic and a lower-cost biosimilar, the 6% mark-up could offer an incentive for physicians to choose the more expensive treatment option. To level the playing field, Congress included a new payment provision for biosimilars – a biosimilar will receive its own ASP, plus 6% of its reference biologic’s ASP. By using the exact same dollar amount mark-up for the innovator and the biosimilar, the intent is to eliminate an incentive to choose the costlier product.

Eventually, with approval of interchangeable biosimilars, the Medicare program may choose to establish volume-weighted ASPs in the same way they currently do for multi-source small molecule drugs covered under Part B. There are no specific provisions for this in the law, so it is unclear if this is the patch Medicare will ultimately take. In the meantime, the law establishes payment across all biosimilars covered under Part B, regardless of an interchangeable designation by the FDA. Volume-weighted, multi-source ASPs would be a step beyond this.

The payment rate for biologics and biosimilars has a direct impact on Medicare beneficiaries, as patients are responsible for 20% coinsurance for all Part B services, including Part B drugs and biologics. Less expensive biosimilar products will translate to lower out-of-pocket costs for Medicare patients, but only if their physician chooses to administer the biosimilar instead of the innovator biologic. However, the vast majority of Medicare beneficiaries maintain secondary insurance (e.g., Medigap) that covers their 20% cost sharing, eliminating their out of pocket costs. As such, many Medicare beneficiaries are not price sensitive of Part B services and treatments. However, for patients without Medigap coverage, cost-sharing for Part B biologics can be extremely high, and the introduction of lower-cost biosimilar options could help alleviate these costs.

Medicare Part D

Medicare covers self-administered drugs and biologics (e.g., pills, simple injections) and products excluded from Part B under its prescription drug benefit known as Part D. Medicare beneficiaries can select among a variety of Part D plans offered in their area through private insurers. Medicare establishes parameters for what each plan must cover and how they structure patient cost-sharing, but there is a wide variety in the cost of plans of coverage each offers.

Part D plans typically use a tiered formulary to manage their members' access to covered drugs and biologics. Three-, four-, and five-tiered formularies are common, with lower tiers being associated with lower cost-sharing and patients' out-of-pocket costs per prescription increasing on higher tiers. For example, a four-tiered Part D formulary may place all generic products on tier 1 and require a \$10 co-pay for these products. Tier 2 would include preferred brand-name products, and require a \$25 co-pay. Tier 3 would include non-preferred brand-name products and patients would be required to pay 20% coinsurance for these drugs. Tier 4 would be for high-cost specialty products for which beneficiaries pay 33% cost sharing. The differential cost-sharing structure helps plans control costs by incentivizing patients to choose the least costly treatment option.

In addition, Part D plans employ a number of strategies to control patients' access to products if they are high-cost, have a significant risk of "off-label" use, or are associated with other risks. Plans may impose quantity limits on products, only allowing patients to be dispensed a limited supply at a given time, with no early refills allowed. This can serve to both control plans' costs and to ensure that patients do not exceed recommended doses in a short period of time (e.g., pain management medications).

To ensure only appropriate patients are being dispensed a drug or biologic for a specific indication, plans can require prior authorization, or a process by which the plan verifies with the pharmacist or prescribing physician that the patient meets the appropriate diagnosis or other criteria to be on the treatment. Plans can also use prior authorization to encourage patients to try lower-cost treatment alternatives rather than a more expensive option if medically appropriate. Similarly, plans can require step-therapy, or a specific progression of products or treatment options that the patient must try before they will cover a more expensive treatment. For example, plans can require that a patient try a generic version of a product prior to approving coverage for a brand-name equivalent.

Given the structure of Part D plans and their current ability to drive patients to lower-cost treatment alternatives, it is likely that biosimilar products will easily fall into the current structures. Whether or not biosimilars will receive the same treatment as small molecule generics by Part D plans remains unclear, and will largely depend on the price differential between the biosimilar product and its reference product, as well as the FDA-label for the biosimilar product. Initially, plans may be hesitant to treat products approved as biosimilar as fully substitutable for the originator biologic, but an interchangeable designation by the FDA may be the bar plans use to evaluate this criteria. Regardless of the availability of interchangeable biosimilars in the near-term, Medicare beneficiaries are likely to see savings from Part D biosimilars in the short-term, since plans will work to move patients to less-costly treatments. In addition, unlike Part B where beneficiaries can purchase Medigap insurance to cover their 20% coinsurance, patients cannot have secondary insurance under Part D. Therefore, patients tend to be more cost-sensitive to Part D products and may choose lower-cost alternatives more readily under Part D than under Part B as they have more control over ultimate dispensing.

Drugs and biologics dispensed under Medicare Part D are also subject to state pharmacy laws. Many states have generic substitution laws which either allow or require pharmacists to dispense the generic version of a product, even if a physician writes the prescription specifically for a brand name product. Since current laws are written for small molecule generics, it is unclear how, if at all, these laws will apply to biosimilars. States may need to revise their current laws or create new laws to guide pharmacists in accepted or required substitution practices for biologics and biosimilars. How states implement these laws will have a direct impact on patient access to biosimilars in the pharmacy setting, as well as their out-of-pocket costs. Different states may choose different approaches and this possibility for distinctions between what is covered and how much the patient's may need to contribute will be important to consider.

Private Insurance Medical Benefit Drug and Biologic Coverage

Similar to Medicare Part B, most private insurers cover physician administered drugs and biologics under their Medical Benefit. Also like Medicare, private insurers typically allow physicians considerable leeway in what products they choose to administer to their patients, leaving clinical decision-making up to treating physicians.

Off-label coverage for oncology treatments is widely available under private insurance much like it is to Medicare beneficiaries. Unlike Medicare which has limited ability to manage drugs and biologics under Part B, private payers typically manage treatments under both the medical and pharmacy benefits, so in cases where there are treatment options that are physician administered or self-administered (covered under the pharmacy benefit, discussed below), private insurers can establish coverage policies that require the use of a self-administered product before a medical benefit product will be covered, or vice versa. Similarly, upon approval of biosimilars, private insurers will have the option of establishing coverage policies that require the use of a lower-cost biosimilar before the brand-name product will receive coverage.

As with Medicare “buy and bill”, for privately insured patients, physicians purchase and stock products which they administer in their office. They then bill the patient’s insurance for the drug or biologic administered. Many private insurers use Medicare’s ASP-based payment rates to reimburse physicians for medical benefit drugs. While private insurers are increasingly using ASP to pay for drugs, many still use a different mark-up percentage than Medicare, with many paying more than Medicare (e.g., 110% of ASP). Since many plans already use Medicare as a benchmark for establishing their payment rates for medical benefit drugs and biologics, it is likely many will follow Medicare’s lead in setting payment rates for biosimilars as well.

Unlike Medicare Part B, private insurers are increasingly using specialty pharmacies as a way to manage medical benefit drug costs and remove physicians’ financial incentives under buy and bill by removing the physician from any financial responsibility for the drug. The specialty pharmacy ships the drug or biologic to the physician’s office, and the physician administers the drug or biologic to the patient. The physician then bills the patient’s insurance for their services and the specialty pharmacy bills the insurer for the drug. By using a specialty pharmacy, private insurers typically are able to pay less for the products than they would under a buy and bill system and they are able to have more control over what products patients receive. Whether or not an insurer requires physicians to use specialty pharmacy or offers it as an alternative to buy and bill varies based on a number of factors and is subject to contracting between insurers and their network of providers.

Private Insurance Pharmacy Benefit Drug and Biologic Coverage

Private insurance plans typically maintain pharmacy benefit structures which are very similar to Medicare Part D. Self-administered products typically dispensed in the retail pharmacy setting fall under plans’ pharmacy benefits, usually via a tiered formulary structure. Unlike Medicare, private insurers have the option to manage all drugs and biologics under one benefit design, whether they are self-administered or require a physician to deliver them. While this is an option, few plans tend to do this.

Similar to Medicare Part D, products placed on lower tiers tend to be associated with lower out-of-pocket costs for patients than products appearing on higher tiers. This structure can help

plans control their costs by incentivizing patients to choose the lowest-cost treatment options. In addition, all drugs delivered in the retail pharmacy setting are subject to state generic substitution laws, regardless of the patient's insurance. As discussed above, it is unclear how current laws may pertain to biosimilars when approved, but states may act to ensure that patients have access to lower-cost alternatives as soon as possible.