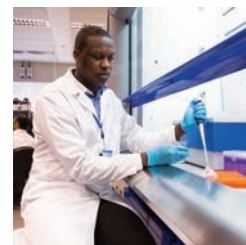


Introduction to Biosimilar Medicines



Research Advocacy Network

Advancing Patient-Focused Research

Introduction to Biosimilar Medicines

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Introduction to Biosimilar Medicines

What are biologics and biosimilars?

Globally, there continues to be growth in the burden of chronic diseases, making it vital for patients to be able to access safe and effective treatment. Biologics are a distinct class of potent medications that have revolutionized the way physicians are now able to treat cancers, diabetes, autoimmune disorders and other conditions. The outcomes for patients have been remarkable. As an example, in oncology, treatment with a biologic has reduced deaths by half for those with non-Hodgkin's lymphoma. Today, there are over 200 biologics and vaccines on the market worldwide and the majority of these products are therapeutic proteins. These are proteins that are engineered in the laboratory for pharmaceutical use — Insulin was the first. To say that this area of medicine is growing may be a bit of an understatement as there are greater than 900 more biotechnology medicines and vaccines currently in development.

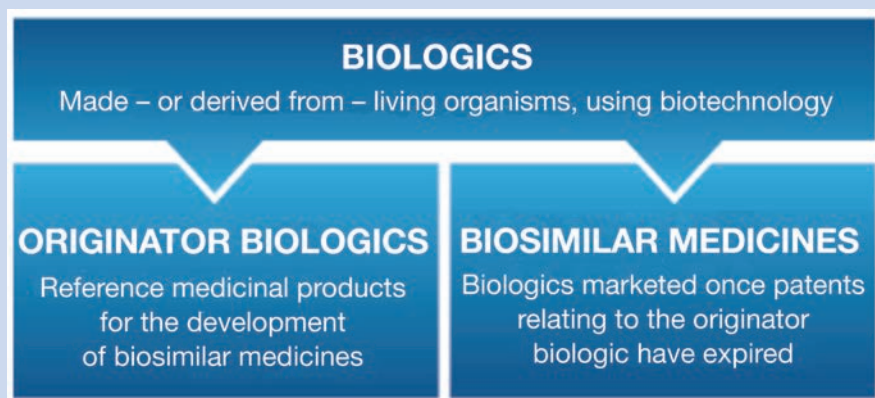
Compared to the more traditional drugs (often referred to as “small-molecule” or “chemical” drugs), such as Aspirin, biologics are inherently more complex, come from living organisms and they cannot be synthesized in the laboratory by chemical means alone. These biopharmaceutical weapons of disease are known by an array of names, including: biological, biologic, biologic therapies, biologic agents, biological response modifier therapy (BRM) or immunotherapy.

Biosimilar medicines or more simply, biosimilars, which may also be known as follow-on biologics or subsequent entry biologics, are developed to be highly similar versions of approved biologics that have reached the end of their proprietary patents.

Biologic: originates from ‘biology’, the science of living organisms. Any of a class of medicines in which the active pharmaceutical ingredient comes from a living organism that cannot reasonably be synthesized by chemical means. Biosimilars are Biologics.

Biosimilars have the potential to allow for patient access to more cost-effective alternatives and may foster a competitive environment for future development of biologic medicines and commercialization. When referring to the original branded and approved biologic product, in the context of biosimilar medicine, it is often called the reference product, originator product or innovator product. A biosimilar has to have demonstrated similarity, meaning no clinically meaningful differences, between itself and its reference biologic product in terms of safety, purity, and potency. The biosimilar and its reference product usually have the same primary structure and other molecular similarities, but minor differences in the clinically inactive components may exist. Please don't make the common mistake and think, “biosimilars are generics of biologics.” Biosimilars aren't generics, because generic drugs are copies of brand-name drugs, have the same active ingredient, and are precisely the same as their brand name drugs in dosage form, safety, strength, route of administration, quality, performance

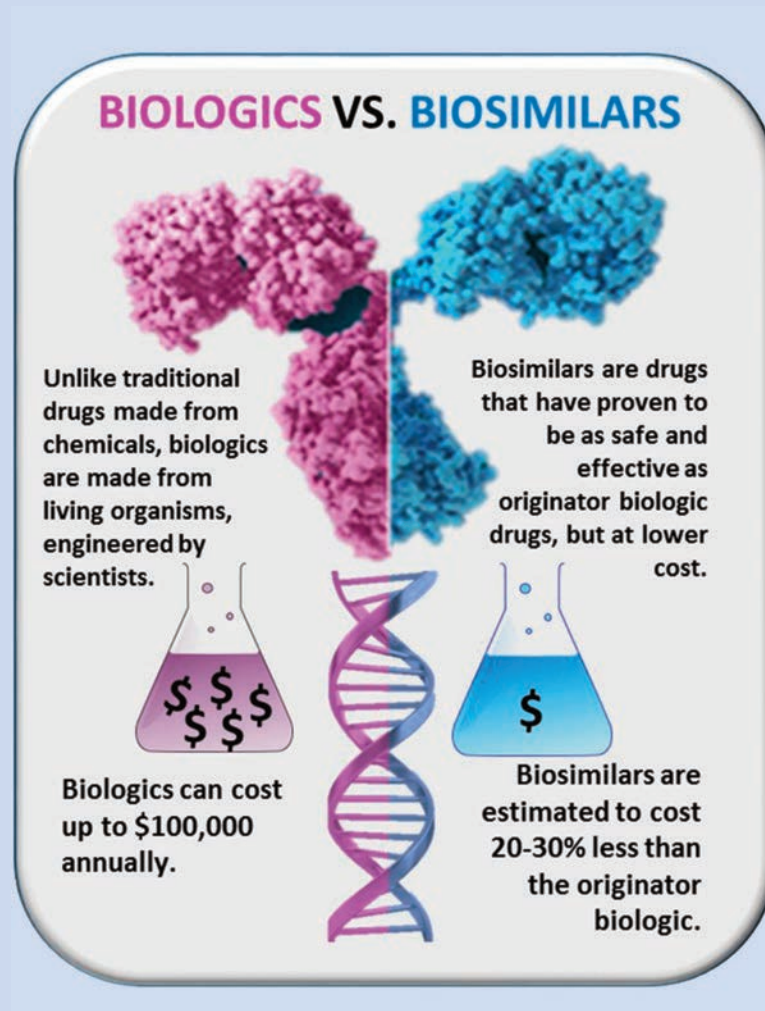
characteristics and intended use. That means the brand-name and the generic are ‘bioequivalent’. Biosimilars are ‘highly similar’ to the reference product they were compared to, but have allowable differences because they are made from living organisms — this is key. We will explore this in greater detail in Chapter 2.



Modern biologic medicines have demonstrated improved health outcomes for patients, however barriers to access still exist, one of the greatest being cost. In the coming years, the patents and exclusivity protection of many well known biologics are set to expire, and biosimilar medicines are emerging as an alternative treatment choice. Also, a somewhat attractive alternative treatment choice, because biosimilars are typically made available at a lower cost, improving accessibility and providing greater opportunity to patients, their doctors and the healthcare system overall.

In this tutorial we will explore what makes biologics different than small-molecule drugs, (eg. Aspirin, Lipitor or Celebrex), how they work in our bodies and against disease, and how biosimilars are similar, and not so similar, to their originating biologic products. We will discuss the manufacturing processes of biosimilars, the challenges with regulating these types of medicines and how the regulation practices differ around the world.

Our aim is to provide unbiased information that can help patients and their healthcare team to make well informed decisions regarding the use of biosimilars in their health care plan. We will also explore how this information can be useful to patients, healthcare stake holders and patients' organizations.



Chapter 1: The Basics of Biologics

Goats are among the most beloved, and adorable farm residents, well known for their antics and producing the milk that gives us the most delicious cheese. Now, thanks to genetic engineering, some goats are making more than cheese, they are a key part of creating important medical treatments.

The term "pharming" comes from a combination of the words "farming" and "pharmaceuticals." It's a melding of the most basic methods of agriculture with the most advanced biotechnology. Scientists are able to alter an animal's own DNA, or to splice in new DNA, called a transgene, from another species. These transgenic animals can then be used to make human proteins that have incredible medicinal value.



Some human proteins that are used as drugs require biological modifications that only the cells of other mammals, such as cows, goats, and sheep, can provide. For these drugs, production in transgenic animals is a good option. Using farm animals for drug production has many advantages because they reproduce quickly, have flexible production, and are easily maintained.

How are scientists able to get these adorable goats to part with their valuable proteins? They simply milk them. It's true. It's just about the best way to recover large quantities of a protein encoded by a transgene. More importantly, since the mammary gland and milk are not part of the main life support systems, there is little risk of harm to the animal that's making the transgenic protein. She can carry on being a happy goat, likely unaware that she has contributed to biologics such as ATryn, an anti-blood-clotting protein, or Ruconest, a protein that treats rapid tissue swelling. A female goat can produce up to 150 to more than 200 gallons of milk per year that can yield nearly 9 pounds of these treasured proteins annually.

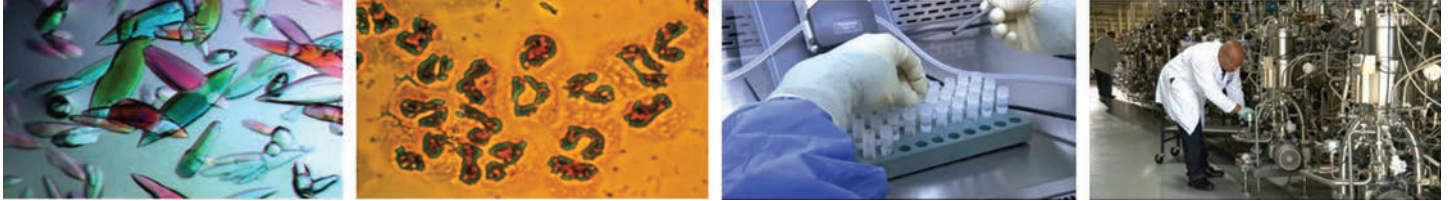
In this chapter we will explore how living organisms and technology have created biologics and biosimilars and revolutionized how many diseases and disorders are treated.

Let's Start with Biotechnology

Biotechnology describes how scientific and engineering methods are applied in order to manipulate living organisms, such as bacteria or yeast, in order to produce goods and services. The term biotechnology came into use in the early 20th century and was initially directed towards improving food production, however it soon expanded into medical uses. The early work in microbiology by Louis Pasteur, Edward Jenner's pioneering of the world's first vaccine against smallpox, innovations in antibiotics, and the uncovering of the structure of DNA all served as building blocks for biotechnology. In the same way penicillin greatly impacted countless lives over a half-century ago, today's biologic medicines are as significant to patients with serious illnesses. In this exciting field, scientists and engineers focus their skills on harnessing the natural process of cells, viruses, and other microscopic living organisms and alter the genetic make-up of the organisms to bring about specific results.

As early as the 1970s, scientists were using genetic engineering techniques, manipulating the genes of living organisms such as plant or animal cells, bacteria, yeast and viruses, to make therapeutic proteins.

Over the past 30 years, there has been tremendous growth and development of biologic agents in the pharmaceutical industry. The National Cancer Institute has defined a biologic drug as “a substance that is made from a living organism or its products and is used in the prevention, diagnosis or treatment of cancer and other diseases”



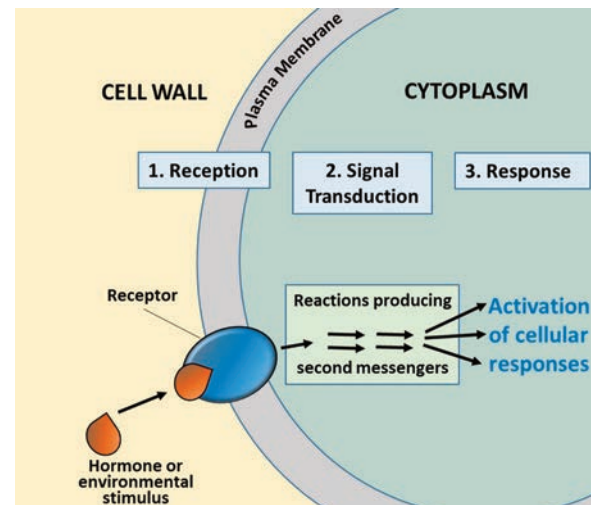
The “Bio” in Biologic and Biosimilar Agents

Biological products have transformed the diagnosis, prevention, cure and management of a wide range of serious and chronic diseases. What makes them different from the more traditional, small-molecule drugs (like acetaminophen or acetylsalicylic acid [aspirin]) is that biologic agents are found naturally in your body and may include things like sugars, proteins, nucleic acids, or specific cells or tissues. Biologic medicines are created when different doses or formulations of these naturally occurring agents are used to treat diseases, like cancer. Biosimilars are a relatively new entity, making our discussion quite timely, with the very first approved for use in Europe in 2006 and very recently, 2015 in the United States. Biologics are not new; development of human growth hormone, insulin, and red-blood cell stimulating agents occurred decades ago. Prior to 1982, diabetic patients had to use insulin extracted and purified from the pancreas of cows or pigs. Scientists subsequently discovered how to modify cells to cause them to express insulin in the laboratory, allowing for insulin to be manufactured and provided to patient using this new method.

Scientific fields used in developing biologics include genomics and proteomics, as well as microarray, cell culture, and monoclonal antibody technologies. The disease targets for the biologics of today have increased exponentially with new genetic information and new understanding of disease processes. We can look deeper into the disease or condition and learn what is happening inside each of our cells, and further, to the components that make up each cell. Increasing knowledge of genetics and cell processes leads to potential new biologic (and drug) targets at each step in the protein-production process. This opens the door to new, incredibly specific therapies, which in turn lead to better understanding of diseases.

Getting to the Cell of the Matter

A biochemical cascade (or a signaling pathway) is a series of chemical reactions which are started by a stimulus (first messenger) acting on a receptor. Think of a line of falling dominos. The receptor is linked to the inside of a cell through second messengers (which amplifies the initial signal). These second messengers take this amplified initial signal ultimately to effector molecules, resulting in a cell response to the initial stimulus. At each step of the signaling cascade, various controlling factors are involved to regulate the actions and responses of the cell and its components.



Unlike most of the small-molecule drugs that have a specific and known structure, most biological products are complex mixtures that are not as easily identified or characterized. This is the key reason why they are so difficult to make ‘similar’ versions of.

Biologics are developed using a number of different processes, which we will explore in greater detail in Chapter 2, but the key is that they all use biological or natural sources, produced by, or extracted from, living organisms including humans, animals (like our transgenic goat), yeast and special microorganisms.

Sometimes confusion can arise because some medicinal/pharmaceutical products made from biological sources are not biologics. As an example, melatonin is a substance found in animals, plants, fungi and bacteria, so you may think, "A Ha! Melatonin is biologic!" But here is another key distinction, if the biological source (plant animal etc.) is harvested or collected from the source and then manufactured in bulk using industrial scale chemical synthesis, they are then considered synthetic, not biologic. Biologics tend to use biological sources at their sub-cellular level (proteins, genes) and undergo highly complex manufacturing processes.

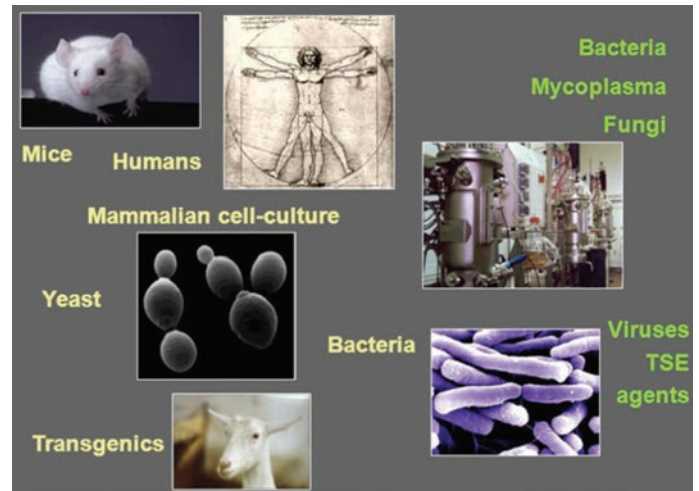


Image provided by the US Food and Drug Administration (FDA).

Some examples of biopharmaceutical products and medicines that are made from biological agents include:

- Insulin for diabetes
- Vaccines to prevent many diseases, like shingles or the flu.
- Hormones for hormone replacement and deficiencies, such as growth hormone disorders
- Monoclonal antibodies for the treatment of cancers and autoimmune diseases
- Blood products and transfusions, such as in the treatment of hemophilia
- Immunomodulators that help to regulate or normalize the immune system, such as beta-interferon for multiple sclerosis
- Enzymes used to remove blood clots
- Botox has both dermatologic and neurologic uses

Official Definitions of Biosimilars

The European Medicine Agency - A biosimilar is a biological medicine that is developed to be similar to an existing biological medicine (the 'reference medicine'). When approved, a biosimilar's variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.



The United States Food and Drug Administration - A biosimilar is a biological product that is highly similar to a US licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product.



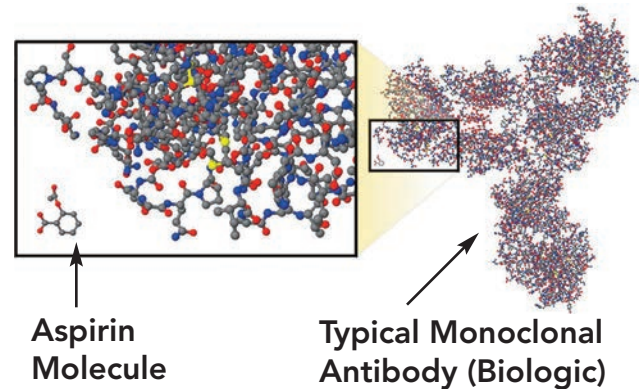
The World Health Organization - A biosimilar is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.



Biologics and Biosimilars are Very Different Than Small Molecule Chemical Medicines

Structural differences

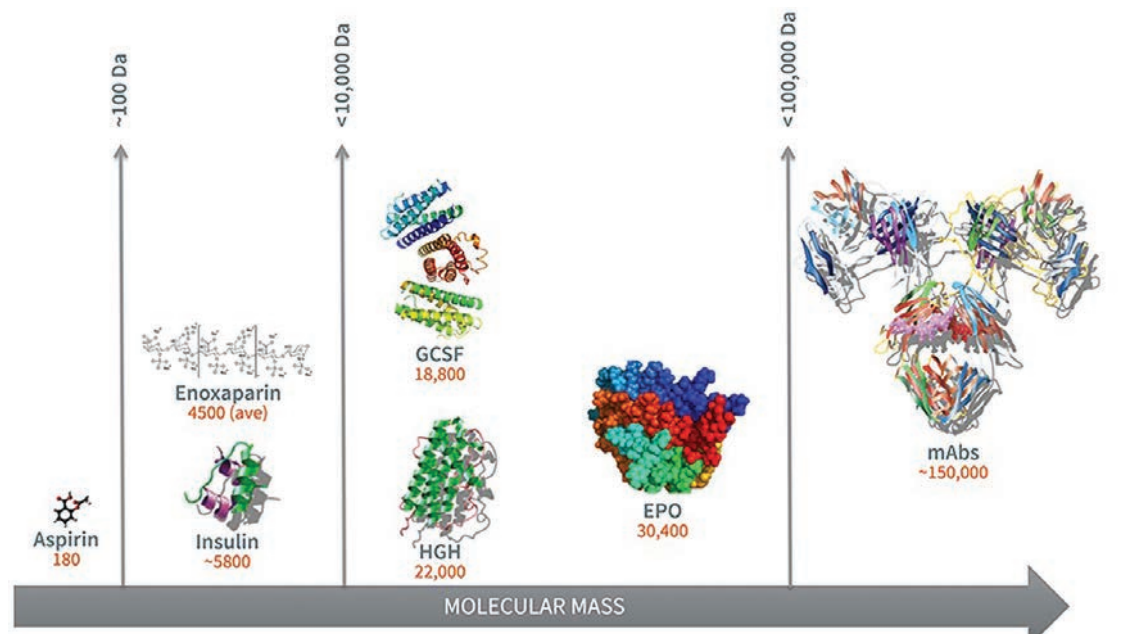
Biologics are larger and much more complex than conventional small-molecule chemical drugs. "If creating a generic drug is like designing a tricycle, then a biosimilar is like building a spaceship, in terms of complexity and size," said Asthika Goonewardene, a senior healthcare analyst with Bloomberg Intelligence. We can easily see this increased level of complexity if we look at the chemical structure of aspirin, a well known, common chemical medicine as compared to the structure of a typical monoclonal antibody, a biologic agent.



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This large and intricate structure is one reason why it is not possible to produce an exact copy of a biological medicine. Another reason is that they are produced using living organisms and that they are very dependent on the specific steps of their manufacturing process. Due to these factors, no two biological medicines can be considered exactly the same, and a degree of variability is natural in all biological medicines. This variability exists between manufacturers, as well as within different batches of the same brand of any biological medicine or when production processes are improved or altered in any way.

In addition to being more structurally complex, biologics are much larger, often 200 to 1,000 times the size of a small-molecule or chemical drug. Unlike small-molecule drugs, biologics do not easily penetrate cell membranes and are not very stable in the stomach and intestines (the gastrointestinal system). As a result, and due to their large size, complexity and sensitivity, biologics are most often injected or delivered intravenously by infusion in a specialized clinic or hospital setting.



GCSF: Granulocyte Colony-Stimulating Factor; HGH: Human Growth Hormone
EPO: Erythropoiesis-stimulating agent; mAbs: monoclonal Antibodies

Biologics can cost thousands of dollars per treatment, and are often less stable than chemically derived drugs, so in order to maintain their safety, purity, and potency they require specific handling and storage conditions, as indicated in the product labeling. Any deviation from the strict light and temperature limits or even unintended jostling or shaking of a product can destroy the protein structure and spoil the drug. A very expensive consequence of mishandling.

The Immune Response

This complexity and increased sensitivity that biologics have to factors such as manufacturing, storage and handling also lead to an increased chance that your body may launch an attack against them, more so than with small-molecule chemical medicines. This is called your immune response. The immune response is how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful.



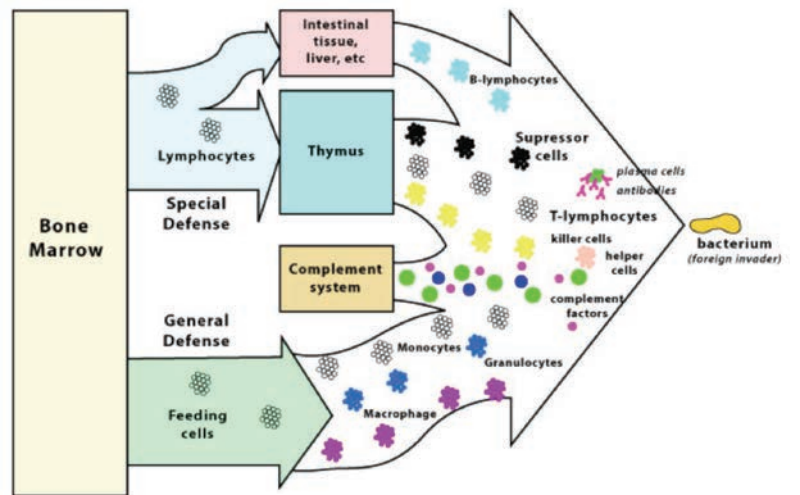
The immune system is very complex and includes:

- White blood cells (WBCs) circulating in the bloodstream
- The tonsils and adenoids in the neck
- The thymus gland in the chest
- The spleen in the abdomen
- Some cells in the liver and bone marrow
- Lymph nodes, many of which are in the neck, underarm, abdomen, and groin
- The lymphatic vessels and fluids

WBCs are the primary players in the immune system response. Some WBCs, including macrophages and natural killer cells, patrol the body, seeking out foreign invaders and diseased, damaged, or dead cells. These white blood cells provide a general—or nonspecific—level of immune protection.

Other WBCs, including cytotoxic T cells and B cells, act against specific targets. Cytotoxic T cells release chemicals that can directly destroy microbes or abnormal cells. B cells make antibodies that latch onto foreign intruders or abnormal cells and tag them for destruction by another component of the immune system. Still other WBCs, including dendritic cells, play supporting roles to ensure that cytotoxic T cells and B cells do their jobs effectively.

An immune response can take many forms, often causing an array of flu-like symptoms, including fever, chills, weakness, dizziness, nausea or vomiting, muscle or joint aches, fatigue, headache, occasional breathing difficulties, and lowered or heightened blood pressure. Biological therapies that provoke an immune system response also pose a risk of severe or even fatal hypersensitivity (allergic) reactions.



Used with permission from Sonya White/Healthy Thyroid Center.

The likelihood that your body will want to launch this immune response is referred to as immunogenic potential. Having a higher immunogenic potential means that there is a greater likelihood that the biologic medicine can prompt an undesired response from the body's immune system, which can also be called immunogenicity.

Immunogenicity

Immunogenicity is a measure of the immune response to a therapeutic drug. Due to the large size of the biologic molecule, it is always recognized by the human immune system, whereas a small molecule drug could travel through the body unnoticed and rarely cause an immune reaction or response. Thus the risk of an immune response from a biologic is much more significant than with small molecules. Immunogenicity is a well recognized safety concern for patients receiving biologics and biosimilars.

An immune response may appear as a hypersensitivity or allergy to the drug and the likelihood of such a reaction may be influenced by even the smallest changes in the drug's production methods or if any impurities are present. This means that if a patient receives a biologic and has no reaction, there is no guarantee that they will not have an immune response another time, using the same product.

HOW ARE BIOLOGIC MEDICINES DIFFERENT?

| Small Molecule Drugs (example: acetaminophen) | Biologics (example: trastuzumab (Herceptin)) |
|--|---|
| Generally low molecular weight | Generally high molecular weight |
| Often an oral solid (tablet or pill form) | Often an injection or IV infusion |
| Usually dispensed by retail pharmacies | Often dispensed by physicians or hospitals |
| Usually organic or chemically synthesized | Made with/from live cells/organisms → inherent & contamination risk |
| Fewer critical processing steps | Many critical processing steps |
| Well-characterized | Less easily characterized |
| Known structure | Structure may or may not be completely defined or known. |
| Homogeneous drug substance (same throughout) | Heterogeneous mixtures → may include variants |
| Usually not immunogenic | Often immunogenic |

Use of Biologics in Cancer Treatment

In oncology, biologic agents can be a vital piece, or rather pieces, of the treatment plan. For patients with cancer, biological therapies (like trastuzumab) may be used to treat the cancer itself or the side effects of other cancer treatments (like erythropoietin for low blood counts). Patients may receive a single biologic or a combination of two or more agents at one time. They may even receive these medicines alongside chemotherapy, radiation therapy, or surgery. Biologics can be given to patients in a number of different ways and may include needle injection into the skin or veins, or injection into an organ or cavity of the body using special procedures.

In the previous section we discussed immunogenicity and how biologics may cause an undesired immune response, but some biological therapies use vaccines or bacteria to stimulate the body's immune system to act against cancer cells. These types of biological therapy, which are sometimes referred to collectively as "immunotherapy" or "biological response modifier therapy," do not target cancer cells directly.

The Good Immune Response

In cancer treatment and in other diseases, biological products help the immune system function better. As we mentioned earlier, the immune system is our body's defense structure and is made up of organs and cells throughout the body that work together to keep us healthy. The immune system defends our body against bacteria and viruses that can cause infection. It also helps find and destroy damaged and abnormal cells, like cancer cells. When bacteria, a virus, or an abnormal cell is present, the immune system reacts with an "immune response". We have shown that there are different types of WBCs, they all work together with other parts

of the immune system to keep you healthy. Some WBCs directly attack bacteria, viruses, or abnormal cells (like cancer cells), while others work by releasing chemicals that destroy these invaders. All the WBCs work as a team, much like different players on a sports team, they each play a different role, but share a common goal.

In keeping with a sporting analogy, biologic pharmaceuticals are an important part of the WBC team, taking on the role of team coach. These medicines help the WBCs train to become stronger in the fight against bacteria, viruses, and abnormal cells and coach the WBCs to become smarter and to outplay these invaders. Biologics can help patients and their medical team win the battle against cancer.

Other than immunotherapies, other biological therapies, such as antibodies or segments of genetic material (RNA or DNA), do target cancer cells directly. Biological therapies that interfere with specific molecules involved in tumor growth and progression are often referred to as targeted therapies. You can find much more detail about targeted therapies in the Research Advocacy Network tutorial, *Targeted Therapies in Cancer*.

Examples of Some of the Types of Biologics Used in Cancer Treatment are:

- ▶ Monoclonal antibodies (MoAb)
- ▶ Cytokines - Interferon (IFN), Interleukin (IL) & Hematopoietic growth factors
- ▶ Colony stimulating factors (CSF)
- ▶ Vaccines
- ▶ Bacillus Calmette-Guérin (BCG)

Monoclonal Antibodies

Biotechnology has contributed to significant advances in cancer treatment, including hormone therapies, biologics and targeted therapies such as monoclonal antibodies (mAbs) that have revolutionized oncology supportive care for immune-compromised patients on chemotherapy. Supportive care is given to improve the quality of life of patients by preventing or treating symptoms of the disease, or side effects caused by treatment.

Even though vaccines and insulin are also biologics, monoclonal antibodies have the unfortunate distinction as the most expensive type of biologic drug. First released in 1986 for the treatment of cancer, monoclonal antibodies are the most rapidly growing type of biologic drug. That's because they are extremely targeted therapies that block specific interactions in the immune system, which regular drugs can't do.

Monoclonal antibodies are large proteins that are produced by clones of the same living cell, normally created from a rodent's spleen. When these proteins enter the bloodstream, they're able to attach like a puzzle piece to only a few types of cells, such as a protein that is present on the surface of cancer cells but is absent from (or expressed at lower levels by) normal cells. This is called a lock-and-key mechanism. Because many types of cancer cells grow by the same mechanisms as other diseases, monoclonal antibodies that were originally developed for cancer are now being tested to treat autoimmune disorders, such as adalimumab (Humira) or etanercept (Enbrel) for rheumatoid arthritis and psoriasis, and natalizumab (Tysabri) for multiple sclerosis and Crohn's disease.

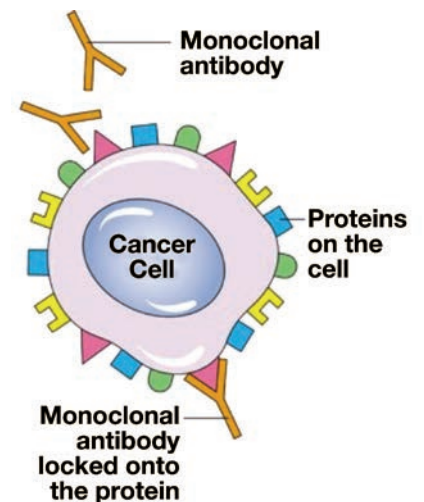


Diagram showing a monoclonal antibody attached to a cancer cell.

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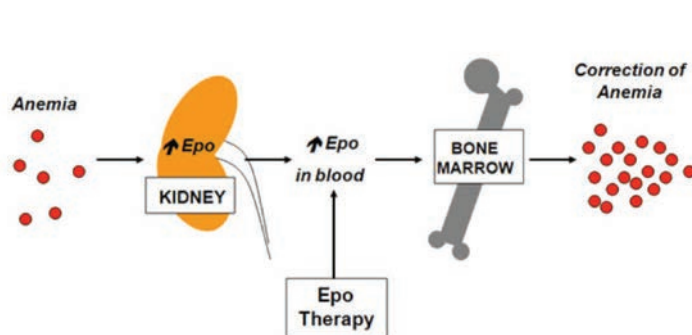
Cytokines - Interferon (IFN), Interleukin (IL) & Hematopoietic Growth Factors

Cytokines are signaling proteins that are produced by white blood cells. They help mediate and regulate immune responses, inflammation, and hematopoiesis (new blood cell formation). Two types of cytokines are used to treat patients with cancer: interferons (IFNs) and interleukins (ILs). A third type, called hematopoietic growth factors, is used to counteract some of the side effects of certain chemotherapy regimens.

Studies have shown that one type of IFN, IFN-alfa, can enhance a patient's immune response to cancer cells by activating certain white blood cells, such as natural killer cells and dendritic cells. IFN-alfa may also inhibit the growth of cancer cells or promote their death.

Like IFNs, ILs play important roles in the body's normal immune response and in the immune system's ability to respond to cancer. Researchers have identified more than a dozen distinct ILs, including IL-2, naturally produced by activated T cells. It increases the production of white blood cells, including cytotoxic T cells and natural killer cells, leading to an enhanced anticancer immune response. IL-2 also facilitates the production of antibodies by B cells to further target cancer cells.

Hematopoietic growth factors are a special class of naturally occurring cytokines. All blood cells arise from hematopoietic stem cells in the bone marrow. Because chemotherapy drugs target proliferating cells, including normal blood stem cells, chemotherapy depletes these stem cells and the blood cells that they produce. Loss of red blood cells, which transport oxygen and nutrients throughout the body, can cause anemia. A decrease in platelets, which are responsible for blood clotting, often leads to abnormal bleeding. Finally, lower white blood cell counts leave chemotherapy patients vulnerable to infections. Several growth factors that promote the growth of these various blood cell populations have been approved for clinical use. Erythropoietin stimulates red blood cell formation, and IL-11 increases platelet production.



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Granulocyte-macrophage Colony-stimulating Factor

WBCs are essential in helping the body fight off infection and chemotherapy treatment for patients with cancer can cause a lowering of WBC count in the body. Colony-stimulating factors (CSFs) are not directly effective against cancer cells, so they are not used to treat cancer. They are used to lessen some of the side effects of cancer treatments. They work to stimulate the bone marrow to increase the production of blood cells. This helps reduce the risk of infection, anemia and bleeding because of low blood cell counts.

Sometimes cancer treatment needs to be stopped or the dose needs to be lowered if blood cell counts are low. CSFs allow people to continue having cancer treatment at the full dose. In some cases, having CSF treatment allows higher doses of chemotherapy or radiation therapy to be given.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) both increase the number of white blood cells, reducing the risk of infections. Treatment with these factors allows patients to continue chemotherapy regimens that might otherwise be stopped temporarily or modified to reduce the drug doses because of low blood cell numbers.

G-CSF and GM-CSF can also enhance the immune system's specific anticancer responses by increasing the number of cancer-fighting T cells. Thus, GM-CSF and G-CSF are used in combination with other biological therapies to strengthen anticancer immune responses. An example of G-CSFs are filgrastims, such as Neupogen (a reference product – original biologic), which stimulates white blood cell production. We know that white blood cells are essential in helping the body fight off infection and the stimulation of white blood cells is important because chemotherapy often causes a lowering of white blood cell count in the body. Due to the high costs associated with Neupogen treatment, it is often used as secondary prophylaxis, meaning after chemotherapy has begun and once white blood cell count has fallen. Since a biosimilar of filgrastim became available in the United Kingdom, at a lower price than the reference product, physicians have started to use it as a primary prophylaxis, meaning from the first chemotherapy cycle to prevent infection and readmission to hospital. Although only recently approved, the hope is that with the approval of the filgrastim biosimilar in the US, practice patterns may also similarly change to reduce the cost barriers and improve patient care.

On March 6, 2015 the FDA approved the very first biosimilar product in the United States, Zarxio (filgrastim-sndz) manufactured by Sandoz, Inc. Zarxio is the biosimilar to Amgen Inc.'s Neupogen (filgrastim), which was originally licensed in 1991.

Zarxio is a granulocyte colony-stimulating factor (G-CSF)

Cancer Treatment Vaccines

Cancer treatment vaccines are designed to treat cancers that have already developed rather than to prevent them in the first place. Cancer treatment vaccines contain cancer-associated antigens to enhance the immune system's response to a patient's tumor cells. The cancer-associated antigens can be proteins or another type of molecule found on the surface of or inside cancer cells that can stimulate B cells or killer T cells to attack them.

Bacillus Calmette-Guérin

Bacillus Calmette-Guérin (BCG) was the first biological therapy to be approved by the FDA. It is a weakened form of a live tuberculosis bacterium that does not cause disease in humans. It was first used medically as a vaccine against tuberculosis. When inserted directly into the bladder with a catheter, BCG stimulates a general immune response that is directed not only against the foreign bacterium itself but also against bladder cancer cells. Approximately 70% of patients with early-stage bladder cancer experience a remission after BCG therapy.

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Chapter 2: Biosimilars are not the Same as Generic Drugs

Some people are very talented when it comes to crafts, especially those with a knack for needle work. Often practical and always beautiful pieces of art are created with knitting needles or crochet hooks. Imagine all of the planning, materials and hours that go into fashioning a blanket of an intricate pattern. The person making it has to find the exact colors and type of wool to use and each loop and stitch of the pattern has to be precise from the beginning, all the way to the end. Rarely are two ever identical, however, given the same pattern and starting materials, they may be similar. So much time, effort, complexity, and precision involved in creating a blanket this way. Or perhaps if you need a blanket, it is much easier to get a generic, mass produced blanket, easy to make, all the same, made for a fraction of the price.



Although a much different process than crocheting, keep in mind that creating a biologic or biosimilar drug takes considerably longer, is far more complex and precise than making a generic mass produced, chemically synthesized drug.

Generic drugs, which are produced by standard chemical synthesis, are very different than biosimilars, whose development is driven by qualities that are unique to living systems. An important distinction is that biosimilars cannot be generic drugs because they are similar (biosimilar), but not identical (bioequivalent) to their reference product.

There are four key things that differentiate a biosimilar from a generic chemical drug:

- Chemical structure
- Analytical characterization
- Complexity of manufacturing process and impact of changes to the process and
- Legislation for the approval of the products.

As we noted earlier, the chemical structure of biologics and biosimilars is far larger and much more complex than conventional small-molecule drugs and their generic copies. The simple structures of small-molecule medicines make them quite easy for new manufacturers to work out how to replicate an identical active ingredient, and create a generic copy. At a pharmacy it is easy to pick up a prescription or buy over-the-counter a branded version (reference, originator product) or its identical generic counterpart, usually at a significantly cheaper price.

With biologics and biosimilars, the small differences are apparent very early in the process. Every manufacturer of biologics or biosimilars uses a unique cell line, which are specific cells that keep dividing and growing over time, under certain conditions in a laboratory. These cells are grown and handled in a unique, proprietary process to generate their distinct biologic agent. Naturally, in the competitive market of pharmaceuticals, the owners of the original reference product keep the processing details a well guarded secret. These factors, the cell line and manufacturing process are the key reasons why it is impossible to produce biosimilars that are identical to the originator

Biosimilarity

Unlikely to have “clinically meaningful” differences between biosimilar and reference product. Recognizes that the two molecules are, in fact, different, but exert highly similar effects.

Bioequivalence

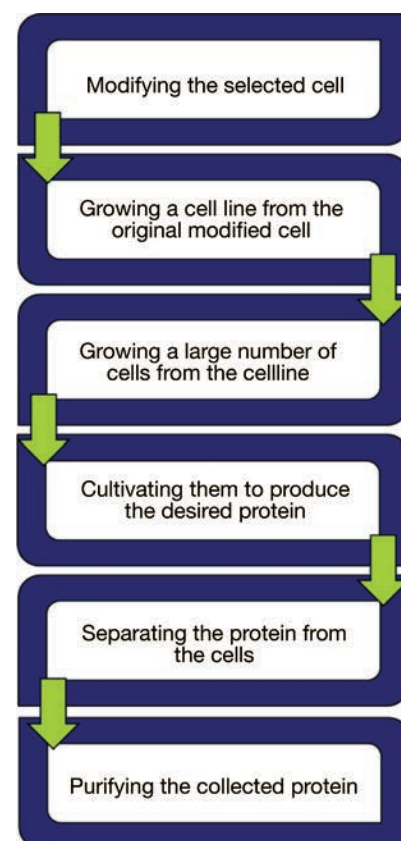
The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

These terms are not equal

drug. Even though the amino acid sequence is essentially the same, slight differences in structure are expected. By contrast, conventional small-molecule drug molecules are much smaller, have a simpler structure, and can be easily manufactured using a controlled and predictable chemical process that generates identical copies to the reference product.

Analytical characterization is a term used to describe whether scientific techniques currently exist that are able to completely define the final chemical structure of a product and compare it to the original reference product. For generic chemical drugs, current analytical techniques are able to ensure that the active ingredient in the generic is precisely identical to its reference product. For biosimilars it is not possible to fully define the final structure, meaning it is not possible to provide a value to report the precise degree of similarity between the product and its reference products. Recall the complexity of the structure as shown earlier.

As we have noted, the manufacturing process for biologics and biosimilars is extremely complex and involves living cells and several stages of production, purification and validation of the final product. Even very small changes in the production process, such as minor equipment or environmental variations, can alter the final structure and function of the protein and the efficacy, safety or availability of the resulting medicine. Generic manufacturing, by comparison, is relatively simple, using medicinal organic chemistry principles and reactions. Small changes within the process are unlikely to cause any alterations to the final product because the end product is identical.



In order to assure the quality and consistency in the final product, the production of biologic and biosimilar medicines requires a high level of monitoring and testing throughout the process. A biologic medicine typically has around 250 in-process tests during manufacturing, compared with around 50 tests for a small-molecule medicine.

Due to these dramatic differences in the complexity between biosimilars and generic drugs, it is easy to see why the regulatory process and approval pathway is far more extensive and intense for biosimilars than generics. The straightforward structure, simplicity of production and analytical methods are part of the reason that generic drugs enjoy an abbreviated, less strenuous regulatory process, including approval through an Abbreviated New Drug Application (ANDA). As it is impossible to produce exact copies of biological medicines, regulators acknowledged that biosimilar medicines required a novel and rigorous testing, approval and regulatory system, different to the approval of generic medicines. Although the biosimilar is not identical to its reference product, it is highly similar, meaning that any differences between the reference product and biosimilar medicines have been shown not to affect quality, safety and efficacy. We will explore the specifics of the regulatory processes in Chapter 4.

Creating a Biologic or a Biosimilar – the Manufacturing Process

The majority of biological medicines are produced using genetically modified cells. These are cells whose genes have been changed, using recombinant DNA techniques (combining DNA from two or more sources), so that they produce a specific substance or perform a function. Genes for a certain protein are introduced into the genes of a host cell (such as a bacteria or yeast cell or our transgenic goat), which would subsequently produce that protein. Each biological medicine manufacturer has its own host cell bank, producing a unique cell line, and develops its own unique manufacturing process.

The manufacturing of biologics is a highly demanding process. As we have seen, protein-based therapies have structures that are far larger, far more complex, and more variable than the structure of drugs based on chemical compounds. Additionally, biological drugs are made using intricate living systems that require very precise conditions in order to make consistent products. Although each product has its own series of intricate parts, overall the manufacturing process consists of these four main steps:

1. Producing the master cell line containing the gene that makes the desired protein.
 - a. The genetic code (a sequence of DNA) of a selected protein (e.g. a hormone, antibody, blood product) is identified and a functional DNA sequence created.
 - b. The genetic code is inserted into various host cell lines (e.g. bacteria or yeast), so that the host cells produce this protein.
 - c. The host cell line that produces the protein the most successfully becomes the chosen host cell line.
2. Growing large numbers of cells that produce the protein in machines called bioreactors; this process is called fermentation.
3. Isolating and purifying the protein, separating it out of the bioreactor via a filtration process.
4. Preparing the biologic for use by patients (stabilising and processing)

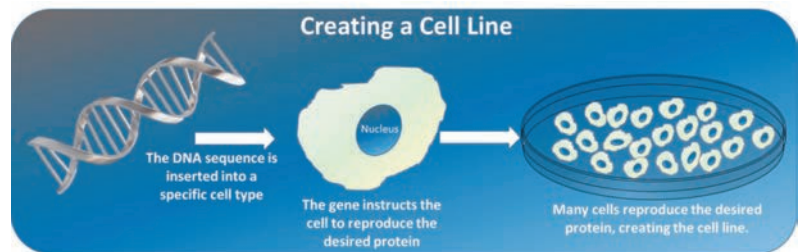


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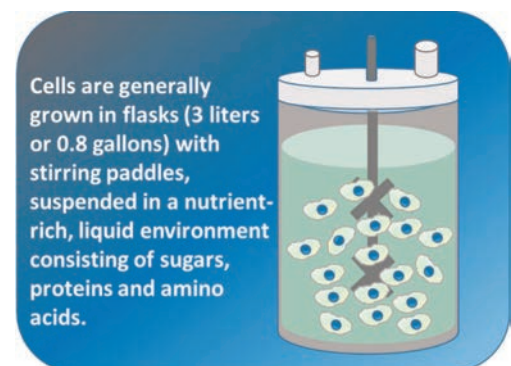
Some biologics can be made using common bacteria, such as E coli. Others require cell lines taken from other biological sources including mammals, which is because many proteins have structural features that only mammalian cells can create. For example, certain proteins have sugar molecules attached to them, and they don't function properly if those sugar molecules are not present in the correct pattern.

In order to create a master cell line, a gene that contains the code for the desired protein is spliced into the biological cell. The gene instructs the cell to produce the desired protein by inducing the cell to produce the protein all on its own.

This newly altered cell is then used to establish the cell line, which consists of thousands of genetically identical copies. Cells are initially placed in petri dishes or flasks containing a liquid broth with the nutrients that cells require for growth, such as sugars, proteins and amino acids.



The manufacturing process begins with cell culture, or cells grown in the laboratory. The environment for growing these cells must be precisely controlled. At every step of this process, it is crucial to maintain the specific environment that cells need in order to thrive. Even subtle changes can affect the cells and alter the proteins they produce. For that reason, strict controls are needed to ensure the quality and consistency of the final product. Scientists carefully monitor such variables as temperature, pH, nutrient concentration, and oxygen levels. They also run frequent tests to guard against contamination from bacteria, yeast, and other microorganisms.

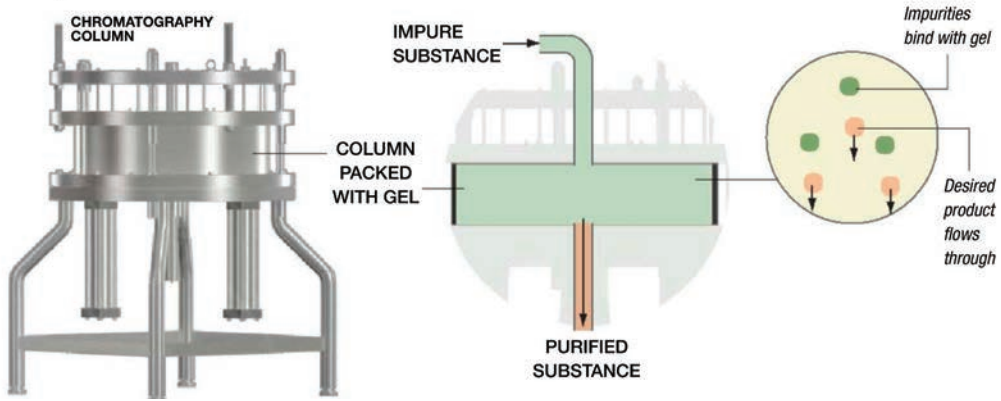


During the scale-up process, the small number of cells from the cell line are placed into 3 liter (0.8 gallon) containers with their growth medium (typically a nutrient rich broth) where they are stirred and kept at optimum conditions for cell growth. When the cells have grown to fill this small container, they are sequentially transferred to larger and larger vessels, called bioreactors. The time spent in each bioreactor varies, depending on the conditions inside, but the average time from small container to large flask take approximately three weeks. Some bioreactor tanks used in manufacturing hold 20,000 liters or over 5000 gallons of cells and growth media. It is in these larger tanks where the cells produce the large amounts of protein that they were originally engineered to produce.



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When the growth process is done, the desired protein is isolated from the cells, the growth media and any other impurities. Various filtering technologies are used to isolate and purify the proteins based on their size, molecular weight, chemical affinity (ability to bind to another) and electrical charge. A common filtering technology is a chromatography column which uses a column filled with a gel substance where the impurities bind with the gel, remaining in the column while the desired product flows through.



The purified protein is typically mixed with a sterile solution that can be injected or infused. The final steps are to fill vials or syringes with individual doses of the finished drug and to label the vials or syringes, package them, and make them available to physicians and patients.

This process is complex and sensitive to change. The physical and chemical properties of the final medicine can be influenced by a number of variables, including changes in the manufacturing process (e.g. the material that the bioreactor is made from), and the handling, packaging, transport and storage processes. Biological products are very sensitive and may be highly susceptible to light and extreme temperatures (requiring controlled refrigeration or frozen storage). These changes could make the medicine less effective and it can be difficult to

ensure consistency from one production cycle to the next. For these reasons, the production of biological medicines requires a high level of technical expertise and the process must be very tightly controlled and monitored to ensure the safety, purity, potency, efficacy and quality of the final medicine.

How Does the Manufacturing Process of Biosimilars Differ?

Because we know that biosimilars are biologics, the manufacturing process for the majority of biologic products is essentially the same, moving through the steps from the creation of the cells to the product in the vial. The development of the cell lines and refining the specifics of the process is what makes biosimilars different and some would say, quite backward.

Rather than starting from what might be considered the beginning of a typical drug development practice, the sequence of manufacturing biosimilars starts at the end, by a process referred to as 'reverse engineering'. This step by step approach, before the manufacturing begins, ensures that the biosimilar product is highly similar to the reference product, in terms of quality, safety and efficacy. Because the manufacturing details of the innovator product are proprietary and a highly guarded secret, the biosimilar is reverse-engineered from its innovator product once its period of exclusivity has expired. This means that the biosimilar developer must acquire the innovator product, work backward from the finished product, using sophisticated analytical tools and existing clinical knowledge, to create their own process that will ensure a resulting product that is highly similar to the original. In the context of biologics and biosimilars the product is highly contingent on the process: the structure, function, and quality of these drugs are the direct result of the manufacturing process by which they were produced.

The structure, function, and quality of biologics and biosimilars are the direct result of the manufacturing process by which they were produced.

For these reasons regulatory agencies, such as the FDA, recognize that a biosimilar cannot be structurally identical to the originator (reference) product because differences in the manufacturing process alter the end product. Rather than requiring that a biosimilar be structurally identical to an originator biologic, the FDA requires that a biosimilar not be "clinically different."

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Chapter 3: Demonstrating Biosimilarity – Principles and Guidance

There are more than a dozen varieties of pinot noir grapes and they produce some of the most popular wines in the world. Even if you were to taste a selection of wines made with the exact same variety the flavors would be different, similar but different. If we have the same type of grapes being put through a fermentation process, how could the results differ? There are several reasons, perhaps the crop used were grown in the temperate climate and frequent rainfall of Burgundy, France or the high temperatures and constant sunshine of California. Even the same variety, grown in the same region may experience variable conditions year over year. Maybe the winemaker decided to make the fermentation process a little longer this year's vintage than last. These are all changes and adjustments made to the growing and manufacturing process, resulting in small differences, even though the end product is still a 'Pinot Noir' the results are similar but not identical.

To make a biologic drug requires a living organism as an agent. In the case of wine, it is yeast and for biologic drugs, the agent may be yeast or bacteria but most often a hamster or mouse cell. Both must be processed using exact ingredients and conditions to achieve the desired outcomes. For both, slight changes in the starting materials and/or the process may lead to very different results. And finally, for both, the outcomes may still vary from "batch to batch" and therefore it is very important to test to assure the product meets quality standards.

Because biologics and biosimilars are produced by living cells (animal, bacteria and yeast) and are also sensitive to minor changes in the manufacturing process. Just as wine grapes that are grown in different regions can result in different tastes, small manufacturing differences can significantly affect the nature of a finished biologic and the way it functions in the body.

Clinical Trials of Biosimilars

A clinical research study measures the effects of new treatments and the study results may be used as part of a regulatory approval process. Clinical trials with biosimilars are different from those done with novel biologic medicines. The fundamental difference is that the goal of a biosimilar clinical trial is to confirm similarity to the originator biologic product and not to prove safety and efficacy all over again.

As per the Declaration of Helsinki, a set of ethical principles regarding human experimentation and research, repeating clinical trials is not permitted because it would be considered unethical. Drug manufacturers are happy to oblige because clinical trials are costly and time consuming, leading to delays of approval for their product.



CLINICAL TRIALS

Clinical trials of biosimilars may pose distinct challenges for the company wanting to have their proposed biosimilar approved. If the goal of a trial is to evaluate biosimilarity, then some patients will receive the reference product and some will receive the proposed biosimilar that is expected to be equivalent, but yet unproven. In these types of trials, physicians and their patients are naturally apprehensive about participating in a trial where no therapeutic improvement is expected than they are already receiving. Patients tend to show more interest in

participating in an oncology clinical trial of a new therapy, that offers the hope of increased possibility of a cure or better control of the disease. At the early stages, there is also an increased risk that the biosimilar may have a different efficacy, safety or immunogenicity profile than the reference product; this is particularly concerning when the proven therapy, the reference product is already available.

Alternatively, there may be increased interest in clinical trials of biosimilars that are compared to the original reference because the comparison is being made with the known, active reference, rather than having patients receive placebo, or no treatment. Of course it is not permitted or ethical to offer a placebo to a patient when a known treatment is available and the consequences of not providing active treatment could be dire.

Even though The National Comprehensive Cancer Network (NCCN), an alliance of the world's leading cancer centers, has reported that there is a low level of physician and patient interest in participating in biosimilar clinical trials. This may not be true for all clinics and regions such as community-based clinics or in regions with limited resources or access to these types of products outside of a trial setting.

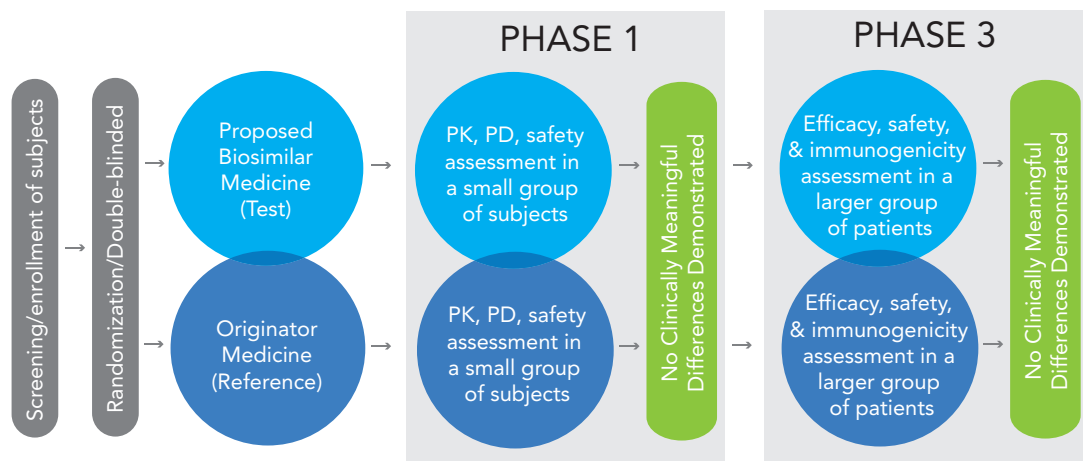
In order to conduct trials of their product, the manufacturers of the biosimilars have to be able to procure multiple batches of reference product with different expiry dates (indicating different batches). This can often be problematic, as the reference companies will likely only release a limited number of batches of commercial stock with different expiry dates over a given period of time. Because the original reference companies would prefer that the biosimilar never be approved or released, they are not going to help facilitate the other company. Therefore, companies pursuing development of biosimilars will need to strategically plan ahead to acquire multiple batches of reference product over a significant time period, prior to the start of development and manufacturing activities.

Clinical trials are conducted in a series of steps, called phases – each phase is designed to answer a separate research question.

Phase I biosimilar studies are referred to as PK/PD (pharmacokinetic/pharmacodynamics) studies. Simply put, pharmacokinetics looks at what the body does to the drug, while pharmacodynamics looks at what the drug does to the body. These studies are designed to demonstrate a similar PK/PD profile of the biosimilar to the reference product. These studies generally involve hundreds of subjects, depending on the molecule being studied. For these early studies, a large quantity of a single batch of the reference product is needed because some variability, be it the biosimilar or reference product, is expected between differing batches of product. This kind of variability can be detrimental to the outcome of a Phase I PK/PD study.

Phase II: The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety. Phase II is often combined with other Phases of study or as an extension of an existing study.

Phase III: The drug or treatment is given to large groups of people as a comparative efficacy study, designed to determine if the investigational therapy is similar to that of the reference product with regards to efficacy and safety. Because Phase III studies involve even larger groups of people, they require the procurement of even larger quantities of the reference product. In this Phase, multiple batches of reference product are acceptable and preferable, so that the biosimilar study can ensure a continued supply of the reference product. The total cost for purchasing the reference product can make up a significant part of the overall study budget. When conducting trials of biosimilars, regulators require that every effort should be made to conduct double-blind efficacy studies. This means that neither the patient, or the treating physician know whether the patient is receiving the biosimilar or the reference product.



"Usually, it is necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference medicinal product in adequately powered, randomized, parallel group comparative clinical trial(s), preferably double-blind." – EMA Guideline Advisory

Ideally, the best way to blind a biosimilar study is to have an exact copy of the container, stoppers, seals, etc., as those of the reference product. This is usually extremely challenging for various reasons including the complexity of the drug container such as drug pens and patent protection issues. If an exact matching container is not possible, then drug may be transferred from an existing container to another, and then packaged and labelled. This can be extremely difficult, knowing how biologics need to be handled and stored in very specific conditions.

How Similar is Similar Enough?

Now that the biosimilar has been developed and manufactured, how can we know that it is 'similar enough' to the reference product? The strict, systematic, step-by-step approach used to create the biosimilar helps to ensure that the biosimilar product is highly similar to the reference product in terms of quality, safety and efficacy.

As we noted earlier, biosimilar products aren't identical to the original products. In fact, FDA's latest biosimilars guidance, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, only contains four levels of similarity:

1. not similar
2. similar
3. highly similar
4. highly similar with a fingerprint-like similarity

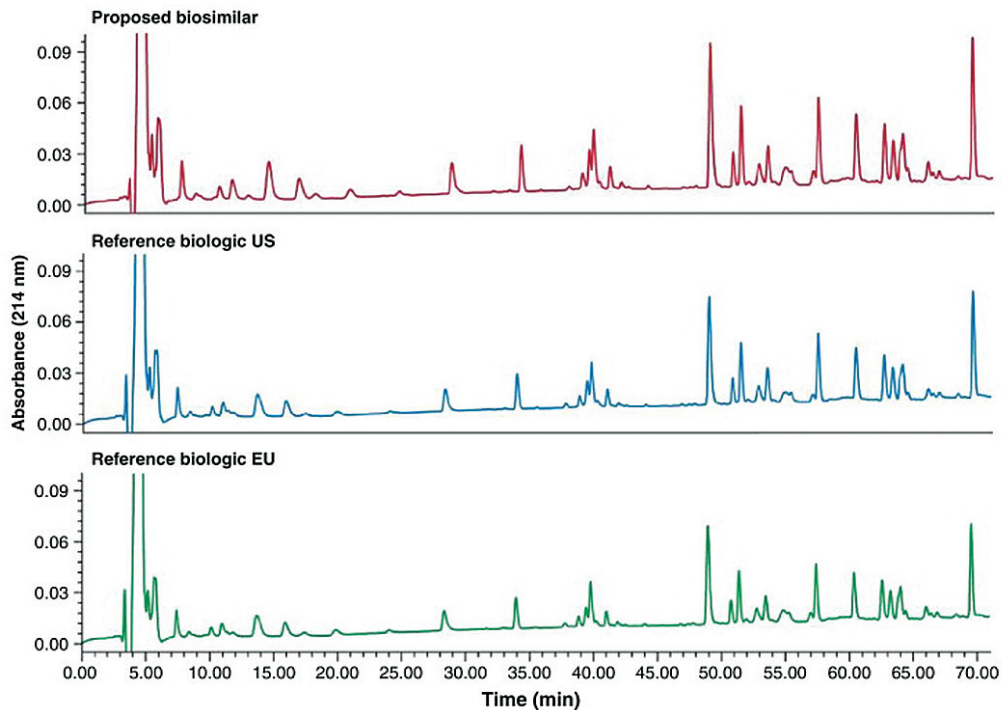
Even the fourth category, "fingerprint-like similarity," isn't quite the same as "identical."

No two biologic products, including those made by the original manufacturer, are identical from one manufacturing batch to the next.

The basic principle underlying the development and approval of a biosimilar medicine is that it is comparable to the reference product. This is assessed through a 'biosimilar comparability exercise'. A comparability exercise is not undertaken to establish the therapeutic benefit of the biosimilar medicine, but to show that it is highly similar to the reference product and that there are no significant differences to its quality, safety and efficacy.

Once the biosimilar medicine is produced, in order to demonstrate biosimilarity, it is compared to the reference product in a biosimilar comparability exercise. There are three steps in the comparability exercise: Quality, Non-Clinical Comparability, and finally Clinical Comparability.

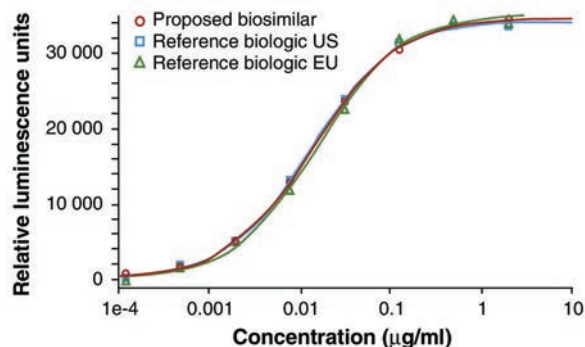
In order to demonstrate comparable quality of a biosimilar product, the physicochemical (physical and chemical properties) and biological qualities are compared through a series of analytical tests. Although many of these differences can be characterized with current analytical techniques, others cannot. The potential for such changes to affect clinical safety and efficacy should be evaluated in clinical trials, as reflected in the current regulatory approval standards for biosimilars. One type of analytical test compares amino acid sequences. The primary amino acid sequence of the biosimilar, for example, is expected to be identical to the reference biologic product, although small differences might be justified if they are not expected to impact efficacy and/or safety. Highly sensitive analytical methods such as peptide mapping can be used to confirm the primary sequence. This is an example of a peptide mapping chromatogram to confirm an amino acid sequence. Very Similar....but not identical.



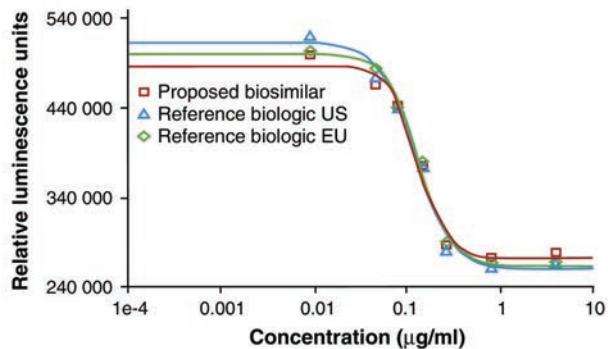
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In vitro functional studies are studies performed with microorganisms or cells and are used to compare the pharmacologic and/or biologic activity of a biosimilar with its reference biologic product. Depending on the type of biosimilar, the number and types of *in vitro* studies required will vary on a case-by-case basis and assessments can include binding and functional assays. Below are examples of a functional assays: inhibition of cell growth and antigen-dependent cellular cytotoxicity (ADCC) with peripheral blood mononuclear cells (PBMC), comparing the proposed biosimilar and its reference biologic products in Europe and the US. Note that the results are very similar....but not identical.

The second stage is non-clinical comparability. This includes dosing studies, and examining what the body does to the drug at different dosages and what the drug does to the body, these are called PK/PD (pharmacokinetic/pharmacodynamics) studies. These types of studies are conducted using appropriate animal models to detect any differences between the biosimilar medicine and the reference product. To show non-clinical comparability, dosing studies are conducted in appropriate animal models to detect any differences between the biosimilar medicine and the reference product.



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Pharmacokinetics looks at what the body does to the drug, while pharmacodynamics looks at what the drug does to the body.

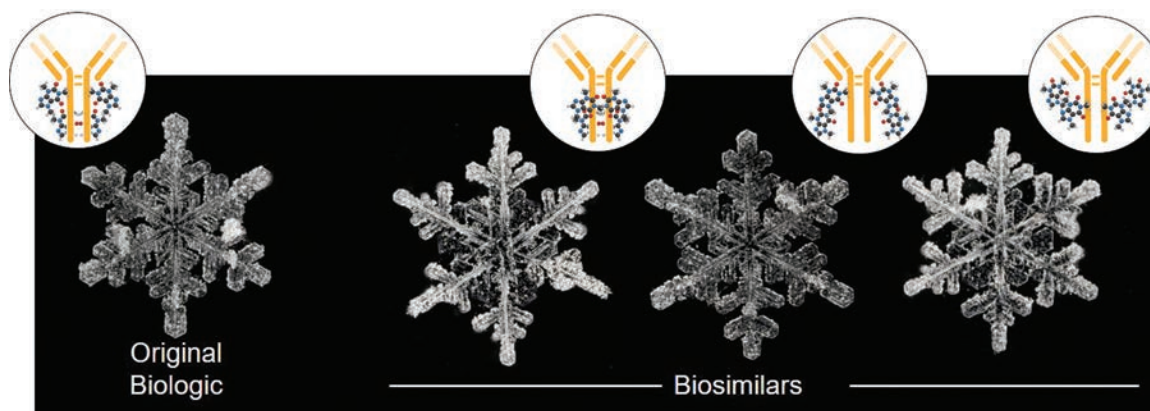
Finally, the third stage is clinical comparability, where the biosimilar medicine is tested in humans in a clinical trial. A comparable safety profile in terms of seriousness and frequency of side effects must also be shown at this point.

How do these three steps all fit together? The non-clinical and clinical comparability provides the confidence that any differences observed at the quality comparability level do not have any impact on the safety and efficacy of the biosimilar medicine. The clinical data is not intended to show the benefit of the medicine, but to ensure that any differences have no impact on its quality and safety. The amount of non-clinical and clinical data needed depends first on how complete the quality data is, and secondly on the product or type of product. Often clinical studies for biosimilar medicines will be smaller (less patients studied) and shorter in duration than those for the reference product.

The clinical data is not intended to show the benefit of the medicine, or that it is any better than the reference product, but to ensure that any differences have no impact on its quality and safety.

Once all the data from the comparability exercise has been collected, it is then submitted to the appropriate regulatory body, along with a plan to manage risk. The plan to manage risk describes the safety profile of the medicine and outlines how the manufacturer will further monitor and fill any gaps in the data regarding safety and efficacy. The regulatory body will assess the comparability data, risk management plan and plans for monitoring after the medicine is made available to determine whether the biosimilar should be approved. We will look into this further in Chapter 5.

A biosimilar product is approved based on showing that it is highly similar to the reference product that is already FDA approved and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products.



Like snowflakes, biosimilars from different manufacturers differ from their reference biologic medicine and from each other. It is critical to understand the differences and to demonstrate that they are not clinically meaningful and thus can be expected to be as safe and effective as the reference product for that approved condition of use.

You may ask, what does the FDA mean by 'Clinically meaningful?' and unfortunately there are no specific regulations or legal requirements defining a minimum or maximum effect size or how to determine a clinically meaningful effect. A simplified definition is that a clinically significant or meaningful difference is the smallest difference that clinicians and patients would care about. Patients themselves may have a very different set of criteria for what medications will have a clinically meaningful impact on their lives. Statisticians, regulators, family members, administrators, and investors all have very different views on what constitutes a 'clinically meaningful effect'.

Any differences in safety between the biosimilar and its reference product are a primary concern. Notably, physicians and patient advocate groups have voiced concern regarding the immune response, for any one patient, may differ unpredictably for different biosimilars that have been developed for the same reference drug.

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Chapter 4: Regulatory Pathways and Guidelines, US and Globally

Despite biosimilars only recently entering the US marketplace, regulation of biological medicines can be traced back over 100 years in the US and it all began with a horse named Jim. Jim was described as an ordinary horse, but he had an extraordinary effect on public health. Some say this retired milk wagon horse spurred the passage of the law that eventually gave the Food and Drug Administration its regulatory authority over vaccines and other biological products.

Unfortunately, Jim's role in this story stems from a tragedy in St. Louis in 1901. At that time, the standard treatment for children with diphtheria was an antitoxin serum made from the blood of horses. Jim had dutifully produced more than 30 quarts of antitoxin in three years, but he was destroyed after contracting tetanus. The serum from Jim's tainted blood was accidentally bottled and used to treat diphtheria patients, causing the death of 13 children in St. Louis. The serum had been manufactured in local establishments with no central or uniform controls in place to ensure potency and purity and there were never any inspections or testing of the final product. Not long after, a similar tragedy occurred in New Jersey when nine children died from tetanus after receiving contaminated smallpox vaccine.

Recognizing the critical need for regulatory safeguards, Congress passed the Biologics Control Act in 1902. Also known as the "Virus-Toxin Law," the act gave the government the first control over the processes used to make biological products, or biologics, and the responsibility to ensure their safety for the American public. The US had its first government regulation of vaccine and antitoxin production.



Image provided by the US Food and Drug Administration (FDA).

The use of biosimilars is increasing worldwide and several different international regulatory pathways have been developed to expedite entry of biosimilars into the global marketplace. The first wave of biosimilar use, specific to oncology, was in Europe and India in 2007. Oncology biosimilars are now widely marketed in several countries in Europe, and in Australia, Japan, China, Russia, India, and South Korea. The notable exception to the global acceptance of biosimilars has been the United States, where by comparison, a number of regulatory and cost barriers to biosimilar approval appear to exist, as evidenced by the very first biosimilar not being approved by the US FDA until 2015.

One of the key missions and responsibility of the US FDA is to protect the health of the US public by assuring the safety, effectiveness and security of drugs and biological products. They are also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.

Regulatory guidance documents developed by the European Medicines Agency (EMA), the US FDA and World Health Organization (WHO) have set out specific principles for showing similarities between biosimilars and reference products. They all require comparability for quality, efficacy, and safety assessments, however the approval of biosimilars are based, in part, on the studies done with the reference product.

The EMA has the longest history in its assessment of biosimilars, dating back to the 2003 EMA regulatory framework, publishing its initial regulatory guidelines in 2005, approving Europe’s first biosimilar products in 2006. US legislation for biosimilars was enacted in 2009 and between 2008 and 2012, Canada, Australia, Japan, India, and South Korea adopted biosimilar regulations that are by and large similar to EMA guidance. China and Russia currently regulate their biosimilars as new biological products, but are looking to develop distinct regulatory pathways for biosimilars. Generally, for smaller countries that may have emerging biosimilar industries, but limited regulatory agencies or pathways, they tend to look to agencies, such as the EMA for direction.

World Health Organization – WHO

In April 2010, the WHO published their Guidelines on Evaluation of Similar Biotherapeutic Products. These guidelines aimed to provide a set of globally acceptable principles to approve biosimilar medicines that would assure quality, safety and efficacy. WHO suggested the Guidelines could be adopted as a whole, partially, or could be the basis for developing a regulatory pathway.

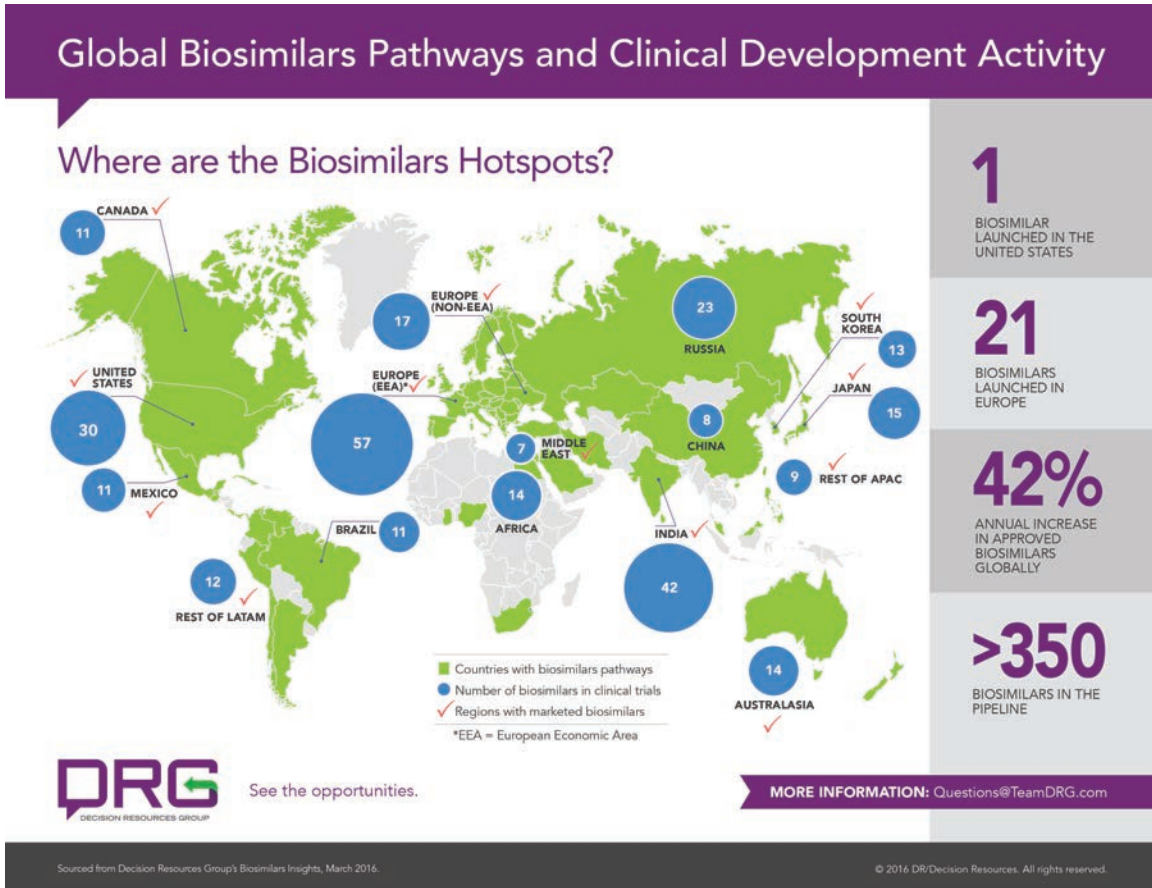


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European Medicines Agency – EMA

The European Union was the first region to set up a framework for the approval of biosimilars in 2003, which began with a directive providing the legal basis in 2001 due to imminent patent expirations for several biologics (epoetin alfa, filgrastim, and somatropin).

The EMA has developed overarching, product-specific, quality, clinical and non-clinical issue guidelines for biosimilars. These are revised on a regular basis by the Biosimilar Medicinal Products Working Party (BMWP) of the EMA to ensure they are up to date and take into account experience with biosimilars and advances in science and technology.

EMA guidelines support an shortened pathway for registration of biosimilar products, basing approval on preclinical and clinical studies that compare the product's efficacy, safety and immunogenicity to the original reference product. The regulatory guidelines are customised for different classes of biosimilar, including different data requirements for nonclinical and clinical studies of recombinant therapeutic proteins, recombinant erythropoietins, interferon b, and monoclonal antibodies.

The EMA requires that the biological reference product has to have been authorized for marketing by the European Union for at least 10 years. This provides a full decade of post-marketing safety and efficacy information to be available for review.

The biosimilar must have the same pharmaceutical form, strength, and administration route (eg. Injection or infusion) as the reference product. EMA guidelines examine manufacturing (quality comparability), non-clinical pharmacology, toxicology, pharmacokinetics, and pharmacodynamics. Clinical considerations, immunogenicity and effectiveness are assessed in safety and efficacy studies using two or three comparative groups and at least one equivalence trial, or a trial that includes the biosimilar, the reference biological, and a placebo, is required. Post approval pharmacovigilance (safety and monitoring after approval – more detail in Chapter 5) and risk management studies are required, because as with all biologic products, many toxic effects may only be detectable after several years. EMA does allow approval extrapolation to other indications (if the reference product works for condition x and y, then the biosimilar can also be used for condition x and y), but these are only considered on a case-by-case basis.

The EMA approval process stresses the importance of rigorous analytical testing of biosimilars and requires that it be supported by appropriate confirmatory clinical evidence to evaluate the clinical impact of minor changes in structure compared with the reference product. An example of this was in the application of a biosimilar candidate (recombinant human interferon a-2a). The EMA began its initial assessment of this product shortly after the application had been submitted in December 2003 in which the manufacturer claimed that analytical testing had shown the product to be similar to the reference product. However, the EMA assessors diligently insisted on further data and eventually determined that the products demonstrated different impurity profiles and the candidate product was refused approval in 2006 based on incomplete and inconclusive data. As well, clinical trials of the proposed biosimilar revealed differences in pharmacokinetics and clinical efficacy (hepatitis C virus infection relapse rate) compared to its reference product.

Over the past decade, the European biosimilar guidelines have been revised to reflect biosimilar experience gained since their initial adoption. The regulatory approval pathway established in Europe is the longest running and is generally regarded as successful which is why it serves as a reference for other national regulatory authorities around the world, including the United States

United States Food and Drug Administration

In the US, the 2009 Biologics Price Competition and Innovation Act (BPCIA) set the FDA framework for biosimilar approvals. The BPCI Act was passed as part of the Affordable Care Act that President Obama signed into law in March 2010 and created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product, called the "reference product." This abbreviated licensure pathway, under section 351(k) of the Public Health Service Act, permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar product to be licensed based on a less than full complement of preclinical and clinical data, specific to that biosimilar product.

A biosimilar cannot be approved in the US until a period of 12 years of market exclusivity for the reference product has passed. However, much like the EMA, a biosimilar product in the US can only be approved by the FDA if it has the same mechanisms of action, routes of

administration, dosage forms and strengths as the reference product, and only for the indications (disease state) and conditions of use that have been approved for the reference product. Guidance documents have stated that indication extrapolation may be possible on a case by case basis.

The facilities where the biosimilar is being manufactured must also meet strict standards and the FDA will resolve any uncertainties related to comparability using physiochemical and functional assays that provide the ability to assess changes in the manufacturing process, and preclinical and clinical studies.

Since 2010, the FDA has released several guidance documents related to the assessment of biosimilars in the US. They outline the approaches needed to assess the molecular structure, function, and toxic effects in preclinical animal studies, the type of human pharmacokinetic and pharmacodynamics studies that will sufficiently demonstrate safety, purity, and potency, and the requirements for showing clinical efficacy, safety, and immunogenicity. All of this evidence will be used to create a risk-based assessment.

Beyond their own requirements, the FDA does take into consideration the protein complexity, manufacturing processes, and studies comparing biosimilars with products that are licensed outside the USA, as well as the pharmacovigilance postmarketing safety concerns. The FDA does have the discretion to review the completeness of this information from other regions and determine if it may allow for some elements of the regulatory procedure to not be needed.

Biosimilars will provide access to important therapies for patients who need them," said FDA Commissioner Margaret A. Hamburg, M.D. "Patients and the health care community can be confident that biosimilar products approved by the FDA meet the agency's rigorous safety, efficacy and quality standards.

The Purple Book

The Purple Book – If you are the manufacturer of a biosimilar, this is the book you want to be in. The Purple Book was launched in September 2014 in anticipation of the impending approval of several new biosimilar products and is the FDA listing of licensed biological products under the Public Health Service Act (the PHS Act) with reference product exclusivity and biosimilarity or interchangeability evaluations.

The lists include the date a biological product was licensed under 351(a) of the PHS Act and whether FDA evaluated the biological product for reference product exclusivity under section 351(k)(7) of the PHS Act. The Purple Book enables a user to see whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar to or interchangeable with a reference biological product (an already-licensed FDA biological product). Biosimilar and interchangeable biological products licensed under section 351(k) of the PHS Act will be listed under the reference product to which biosimilarity or interchangeability was demonstrated.

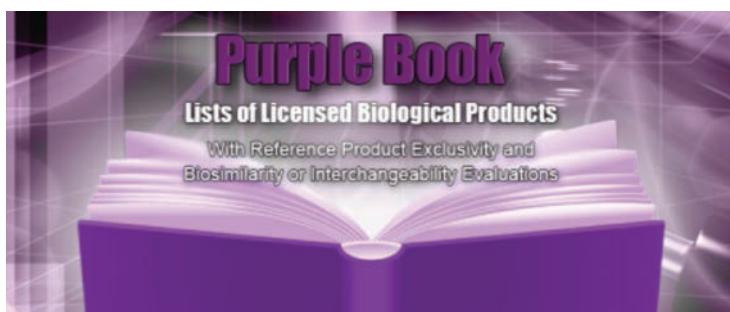


Image provided by the US Food and Drug Administration (FDA).

How does a biosimilar product make its way into the Purple Book? FDA requires licensed biosimilar and interchangeable biological products to meet the Agency's rigorous standards of safety and efficacy. That means patients and health care professionals will be able to rely upon the safety and effectiveness of the biosimilar or interchangeable product, just as they would the reference product.

The book is closely modeled after the FDA's existing Orange Book, a guide containing a list of all pharmaceutical drug products approved for sale in the US after the 1938 enactment of the Federal Food, Drug and Cosmetic Act (FD&C Act). The Orange Book has been primarily used for two purposes: to describe the therapeutic equivalence between two related products and to keep track of patent and marketing exclusivity (more detail about this in Chapter 6). Products that have been withdrawn from sale for reasons of safety or efficacy are not contained within the Orange Book. The book identifies and codes products that are both therapeutically equivalent and therapeutically similar and also contains a list of all approved drugs and the status of their respective patents and marketing exclusivity. This makes it easier for companies to determine when a drug may be legally marketed, assuming they do not violate any additional manufacturing or process patents.

The most obvious difference between the Orange and Purple books is related to the therapeutic equivalence of two products. Because it not impossible to create a biosimilar product that is identical to the original biologic, FDA is instead concerned with biosimilar "interchangeability"—the degree to which two biological products demonstrate the same effects on a patient. In the Purple Book, the FDA can give products two grades: Biosimilar (B) or Interchangeable (I). The latter will, in most cases, be preferable to the developer of a biosimilar.

The first biosimilar product included in FDA's Purple Book was on April 15, 2015, when the FDA declared that Zarxio, the first biosimilar product to obtain approval, is biosimilar (B)—not interchangeable (I).

The "B", means that the FDA found that in its review of the evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data and other clinical safety and effectiveness data that demonstrates Zarxio is biosimilar to Neupogen. If it had been an "I", then under the BPCI Act, it would mean that it could be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

On March 6, 2015 the FDA approved the very first biosimilar product in the United States, Zarxio (filgrastim-sndz) manufactured by Sandoz, Inc. Zarxio is the biosimilar to Amgen Inc.'s Neupogen (filgrastim), which was originally licensed in 1991.



Zarxio can be prescribed, as Neupogen was for:

- patients with cancer receiving myelosuppressive chemotherapy;
- patients with acute myeloid leukemia receiving induction or consolidation chemotherapy;
- patients with cancer undergoing bone marrow transplantation;
- patients undergoing autologous peripheral blood progenitor cell collection and therapy; and
- patients with severe chronic neutropenia.

The most common expected side effects of Zarxio are aching in the bones or muscles and redness, swelling or itching at injection site. Serious side effects may include spleen rupture; serious allergic reactions that may cause rash, shortness of breath, wheezing and/or swelling around the mouth and eyes; fast pulse and sweating; and acute respiratory distress syndrome, a lung disease that can cause shortness of breath, difficulty breathing or increase the rate of breathing.

Interchangeability and Substitution

Interchangeability is a scientific concept that is easy to understand when looking at generic drugs and their original products. The two are proven to be bioequivalent, meaning that they could be swapped for one another (or interchanged) with no perceptible difference in effect to the patient. This interchangeability allows them to be substituted for the original medicine by a pharmacist without seeking approval or even notifying the prescribing physician. Recall that, as we noted earlier, 'bioequivalent' and 'biosimilar' are not the same.

Interchangeability is the determination that a patient can be transferred safely from the innovator/reference product to a biosimilar and expect to have the same experience with no change in safety or efficacy.

Interchangeability is determined and designated by the FDA (or similar agencies in other regions/countries) with the ability to grant marketing approval and authorization. Section 351 of the US Public Health Service (PHS) Act, as amended by the Biologics Price Competition and Innovation (BPCI) Act of 2009, explicitly addresses the issue of interchangeability for biologics and biosimilars (for proteins and peptides comprising more than 40 amino acids), stating that the conditions for a biological

product to be interchangeable with the originator are that the product is shown to be biosimilar to the reference product and that it can be expected to produce the same clinical result as the reference product in any given patient. Moreover, the BPCI Act requires that "for a biological product that is administered more than once to an individual the risk, in terms of safety or diminished efficacy, of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch". Interestingly, even though the FDA considers the possibility of demonstrating interchangeability between biological products, establishing interchangeability in a 351(k) application is scientifically difficult.

Substitution is the legal authority for a pharmacy filling a prescription or hospital to switch the innovator product to the biosimilar or switch the prescribed product to a different product.

Although interchangeability will be determined by the FDA, to further complicate things, the regulation of therapeutic interchange and automatic substitution is controlled by state pharmacy boards and state laws, which vary across the country. Currently, all states allow the physician to specify that a prescription must be dispensed exactly as written ("No substitutions", "Do not substitute" or "Dispense as written"), however if a physician has not made this explicit request, pharmacist substitution practices vary widely by state.

The Alliance for Safe Biologic Medicines conducted a survey of over 350 US oncologists and non-oncologist prescribers and 85% of respondents shared that they would prefer to have the authority to specify that a biologic could not be substituted for a biosimilar, without them having to give the specific instruction as noted above. This authority was considered to be 'critical' or 'very important' by 80% and nearly the same number thought that it was 'critical' or 'very important' that the prescriber be notified if a pharmacist intended to switch to a biosimilar.

If the FDA determines that a product is indeed interchangeable, then the ultimate decisions regarding the clinical use of the biosimilar and policy regarding automatic substitution and notification will be made by medical staff and pharmacy and therapeutic (P&T) committees in accordance with state laws. Because most biologic products need to be carefully handled and are administered directly to the patient by their medical team, substitution is less likely to be a consideration at the community level, retail pharmacy. That is not to say that instances do not exist where biologics are prescribed for supportive care and are intended to be self-administered by the patients, so careful attention must be given at all levels and locations of pharmacy.

Switching: transitioning between the reference product and the biosimilar without the consent of the patient.

Interchangeability: going back and forth between the reference product and the biosimilar with the expectation of achieving the same outcome without the knowledge/consent of the patient.

Substitution: the practice of dispensing one medicine instead of another equivalent without the knowledge of the prescribing physician and the patient.

Extrapolation of Indications

Extrapolation, in the context of our discussion of biologics and biosimilars, is the term to describe using data from previously conducted studies in a particular patient population to justify the use of a drug in another group. This means that biosimilars would be approved for all the same clinical indications (eg: type of tumor, patient status) that the original reference product is approved for, since extensive chemical, physical and biological comparisons have demonstrated that it has similar structure and function. As an example, with scientific justification, a biosimilar that was clinically studied in one tumor type may also be approved for use in another tumor type without new clinical data, because its reference product was newly approved to treat the new tumor type.

The main rationale for the use of extrapolation is ethical, because it is important not to carry out unnecessary clinical trials on humans. But extrapolation also enables drug manufacturers, more specifically the biosimilar manufacturers, to carry out fewer clinical trials thus reducing drug costs and time to get to market.

In April 2015, the FDA released three updated non-binding guidance documents regarding the process for biosimilar approval under section 351(k) of the Public Health Service Act ("PHS Act") as amended by the Biologics Price Competition and Innovation Act of 2009. These documents states that the FDA may extrapolate to an indication that has not been formally investigated for the biosimilar but is approved for the reference product. This means that in general, extrapolation of previous data may be allowed for biosimilars, as long as the manufacturer can demonstrate similar mechanism of action, pharmacokinetics, efficacy, safety and immunogenicity for the new indication or patient population.

In order to support approval of an extrapolated, or new, indication, a biosimilar manufacturer may need to demonstrate that the biosimilar has the same mechanism of action, target-binding characteristics, pharmacokinetics, and biodistribution in the clinically tested and the extrapolated indications, as well as address any expected differences in toxicity or effectiveness.

Concerns have been raised by physicians and even those with biosimilar expertise with regards to the efficacy and safety of biosimilars in extrapolated indications that have not been formally evaluated in clinical studies. The NCCN is apprehensive about applying biosimilar data to support off-label uses (uses that the drug was not originally approved for) and has indicated an interest in developing specific recommendations regarding extrapolation in their future NCCN guideline documents. That said, there have been no reported examples of unexpected differences in efficacy or safety in extrapolated indications for approved biosimilars that have been used in Europe, when compared with their reference products. The European experience of the approved filgrastim biosimilars has shown that they have sufficiently met all of the regulatory requirements there, and have compared favorably with the reference product in efficacy and safety profiles.

Even though there have been no unanticipated differences reported, the European Group for Blood and Marrow Transplantation, as well as the World Marrow Donor Association have expressed concern about potential extrapolation of efficacy data in the mobilization setting to

biosimilar G-CSFs. Stem cell mobilization is a process whereby stem cells are stimulated out of the bone marrow space (e.g., the hip bones and the chest bone) into the bloodstream, so they are available for collection for future reinfusion. The cells are then preserved, frozen and stored until the time of transplant. In this particular case the expert groups have recommended that the biosimilar G-CSF not be used for the mobilization of peripheral blood stem cells (PBSC) for transplantation in normal donors outside of a clinical trial setting because there is a scarcity of safety and long-term follow-up data in this population.

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Neupogen Prescribing Information. Amgen Inc. August 2015

Chapter 5: Ensuring Quality, Safety and Efficacy After Approval

Imagine that a new biosimilar product has just been approved by the US FDA and is now available as a supportive cancer treatment for yourself or a family member at your health care facility. You have read some information about it and your doctor feels quite confident in the clinical data that this may be a beneficial part of your treatment plan. Because you have read that biosimilars are highly similar, but not identical, you ask your doctor if there are any differences that you should be worried about. Your doctor explains that the product has undergone rigorous testing and the facility where it is manufactured has been inspected by the FDA, all to ensure that the product reaching the patients is safe and will act in the way it is expected to.

You wonder though, once the product is approved, is there anyone watching out to be sure that the same high quality there was originally will still be there a year later? Also, what if someone has a bad reaction to this medicine (because you know biological products are very complex), how will you know that the batch you are receiving is safe, or not?

The answers to these important questions are part of the critical work done after a drug has been approved for use. This vigilant surveillance of a drug's performance after it has been approved and released is called Pharmacovigilance.

Evaluating the Scientific and Clinical Data

How do we know that a biosimilar medicine is highly similar to the reference product in terms of quality, safety and efficacy? And what is 'highly similar'?

Earlier we discussed the three steps in the comparability exercise: Demonstration of Quality comparability; Demonstration of Non-clinical comparability and finally Demonstration of Clinical comparability. The results from these exercises contribute to the approval process, but what sort of regulations are in place to ensure that the biosimilar continues to be safe and effective? Because we know that the structure, function, and quality of biologics and biosimilars are the direct result of the manufacturing process by which they were produced, even the smallest change in any part of the process can lead to big safety concerns.

Pharmacovigilance and Safety Monitoring

The WHO recommends that after a product has been approved, the manufacturer should implement a system that is able to detect, assess, understand and prevent any potential drug-related adverse events. Additionally, this system should be able to provide notification of these adverse event occurrences to anywhere the products have been marketed. This system is called pharmacovigilance.

Pharmacovigilance is the surveillance of a drug's performance, particularly of adverse reactions experienced by patients taking the product after it has been released for marketing. It is very important to continue to evaluate the clinical safety of a product after release because, as is the case with most biologics, including biosimilars, all possible adverse events may not have been identified during the approval period.

Pharmacovigilance is the surveillance of a drug's performance, particularly of adverse reactions experienced by patients taking the product after it has been released for marketing.

You may wonder why all the adverse reactions are not identified during the testing phase of a product. Most are, but the safety and efficacy trials are conducted in an 'ideal setting' and study patients are closely monitored and receive the best standard of care available. However,

even when a medicine has shown a good safety profile and efficacy against a disease in a clinical trial, we still do not know if the medicine is fully effective – that is, if it works in the same way in the real world, and how different people may react to it. This is why it is important to keep monitoring the product once it is widely in use.

The overall goal of post-marketing pharmacovigilance plans is to accurately and promptly trace a patient's adverse event to a particular product, manufacturer and lot number. Proper labeling, product tracking and an operational system of reporting and attributing adverse events are all components of a well-functioning pharmacovigilance program.

The key to effective pharmacovigilance is timely information sharing. The information may come from patients and healthcare providers, as well as other sources such as medical literature. Most countries have reporting mechanisms to their regulatory authorities and drug alert systems. When a product is reported to have caused adverse events national authorities analyse the reports and the product and weigh the risks and benefits. They then decide on a course of action, which may include issuing an alert or, in extreme cases, taking the product off the market.

Using Zarxio as an example, because it has been on the market since 2009 in Europe, there are also ongoing pharmacovigilance activities and a non-comparative post-authorization safety study, all of which provided confirmation of similarity in clinical performance to the US FDA prior to its approval in 2015. Since the approval, Sandoz, the manufacturer closely monitors the safety of the product on the market worldwide and summary reports of the post-marketing safety are generated in form of PSURs (periodic safety update reports) on a frequent basis. Labeling remains a concern in the FDA's implementation of biosimilars moving forward, given the fact that no two biologics are identical. We will look at naming and labelling of biosimilars a bit later on in Chapter 7.

The FDA Adverse Event Reporting System

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

The information collected by FAERS is useful to the FDA when looking for new safety concerns that might be related to a marketed product, evaluating a manufacturer's compliance to reporting regulations and responding to outside requests for information. The reports in FAERS are evaluated by clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) to monitor the safety of products after they are approved by FDA. If a potential safety concern is identified in FAERS, further evaluation is performed and if a potential safety concern is identified, FDA may take regulatory action(s) to improve product safety and protect the public health, such as updating a product's labeling information, restricting the use of the drug, communicating new safety information to the public, or, in rare cases, removing a product from the market.

Reporting of adverse events and medication errors by healthcare professionals and consumers is voluntary in the United States. FDA receives some adverse event and medication error reports directly from healthcare professionals (such as physicians, pharmacists, nurses and others) and consumers (such as patients, family members, lawyers and others). Healthcare professionals and consumers may also report adverse events and/or medication errors to the products' manufacturers. If a manufacturer receives an adverse event report, it is required to send the report to FDA as specified by regulations. The reports received directly and the reports from manufacturers are entered into FAERS.

FAERS data are available to the public by a few different methods. Individual safety reports can be requested by sending a Freedom of Information (FOI) request to FDA, or online there is FAERS Statistics, which provides numbers of reports that FDA has received for drug and therapeutic biologic products over the past ten years, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm>, and FAERS Data Files which provides raw data consisting of individual case safety reports extracted from the FAERS database. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm>

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Chapter 6: Patent Protection and Exclusivity

Hiroshi Ueda was a keen photographer, and in the early 1980s, before the days of digital photography, also had the good fortune to work as an engineer for the Minolta camera company. Hiroshi loved to travel and always took many photos of his adventures to show to friends and family. During a trip to Europe, Hiroshi and his wife ran into a bit of a problem, they wanted to have a photo of both of them together, but didn't feel that passers-by couldn't be trusted to take a good photo or even worse, they may steal their camera. "When I was in the Louvre Museum in Paris, I asked a child to take a photo of us, but when I stepped away, the child ran away with my camera," he says.

Hiroshi came up with the "extender stick" - an extendable stick with a tripod screw that was designed for use with a small camera. He even added a mirror to the front of the camera so that photographers could see exactly what they looked like. "The philosophy behind it was that I didn't need to rely on anyone else to take a photo - I could take a picture of myself whenever and wherever I liked."

Hiroshi pitched the idea of this extender stick to Minolta's testing department and encountered some resistance. The idea of taking your own picture was a very new idea and women in particular were very embarrassed by the idea of taking photos of themselves. Despite the doubts, the stick was patented in 1983 but was not a commercial success for Minolta or Hiroshi, even though more than 30 years later he still uses his. The patent, protecting Hiroshi's invention from being marketed and sold by anyone else expired after 20 years, in 2003, as patents do. Unfortunately, this was approximately a decade before the recent boom in selfie sticks. "My idea came too early, but that's just one of those things. We call it a 3am invention - it arrived too early."

Canadian Wayne Fromm is now credited with being the original patent holder of the selfie stick for digital cameras and cell phones. Branded as the Quik Pod, it is a handheld extendable stick for digital cameras and smart phones for taking pictures of one's self. When asked, he said that he was unaware of Hiroshi's earlier design, however in his own patent he does mention the early extender in his patent as "prior art".

So now that the selfie stick has become so popular and created so much revenue, who do you think invented it? Who should receive the credit and the profits from the idea?

In the pharmaceutical, chemical and biotechnology industries patent protection is especially important compared with other industries because it protects the extensive investment in research and clinical testing required before placing it on the market. This investment can be upward of \$1 billion and that doesn't even guarantee the product will be approved or a success. The patent process and exclusivity rules for medicines provides some protection to the company that made the initial investment to recover the development costs and turn a profit before their product can be replicated and can be copied with a fraction of the investment of that required for the original research and clinical testing.

The When, Why & Whom

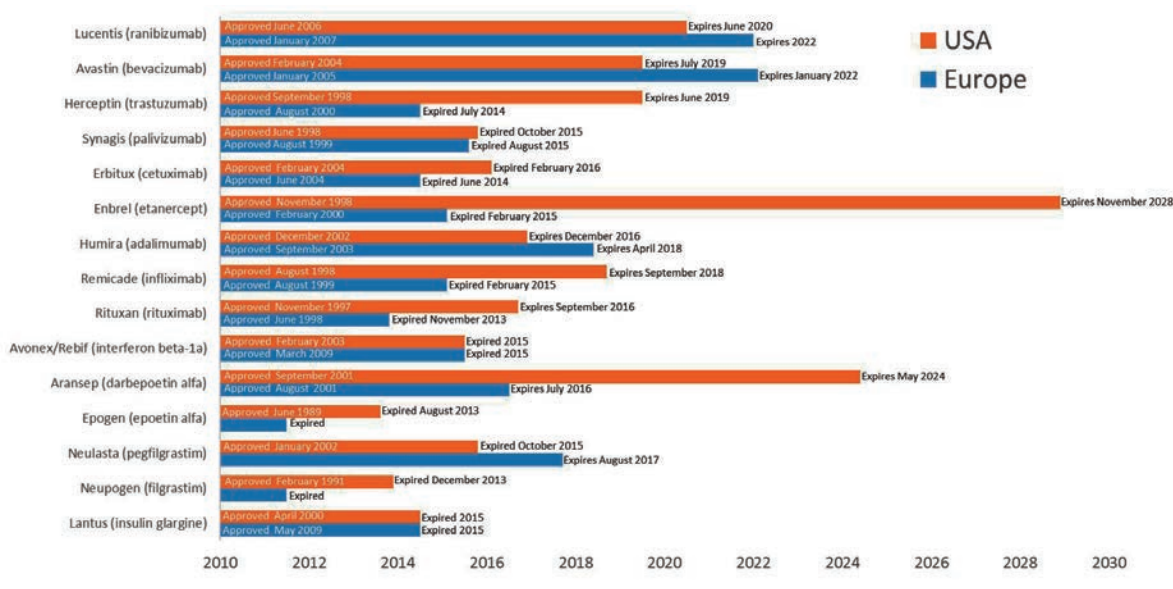
When it comes to drug development and marketing, patents and exclusivity are extremely important to manufacturers and regulators. Although patents and exclusivity work in a similar fashion, they are distinctly different from one another. Patents are granted by the patent and trademark office anywhere along the development lifeline of a drug and can encompass a wide range of claims. Patents can even expire before drug approval, be issued after drug approval,

and anywhere in between. Patents typically expire 20 years from the date of filing, however that can be extended under certain circumstances. The lifetime of a patent varies between countries and also between drugs. If the drug is covered under patent protection, only the pharmaceutical company that holds the patent is allowed to manufacture, market the drug and eventually make profit from it. Often, this patent protection expires before a drug makes its way through approval and onto marketing, and as a result many companies rely on the exclusivity rights granted by regulatory agencies.

Exclusivity describes the exclusive marketing rights granted by the FDA (or other regulatory agency) upon approval of a drug and can run concurrently with a patent or not. Exclusivity is a statutory provision and is granted to the applicant of a new drug application (NDA) if statutory requirements are met. Exclusivity was designed to promote a balance between new drug innovation and generic drug competition. During this exclusivity period, granted after approval, the company that first developed the new drug can market and sell it under a brand name.

Once the period of exclusivity has expired, the drug can be manufactured and sold by other companies. Some would describe this as removing the monopoly, encouraging competition and typically resulting in a significant drop in drug costs. With several exclusivity terms and patents for biologics used in cancer approaching expiration, a number of companies have established biosimilar development programs for therapeutics. These biologic include bevacizumab, cetuximab, rituximab, and trastuzumab and supportive care products such as epoetin alfa, filgrastim, and pegfilgrastim.

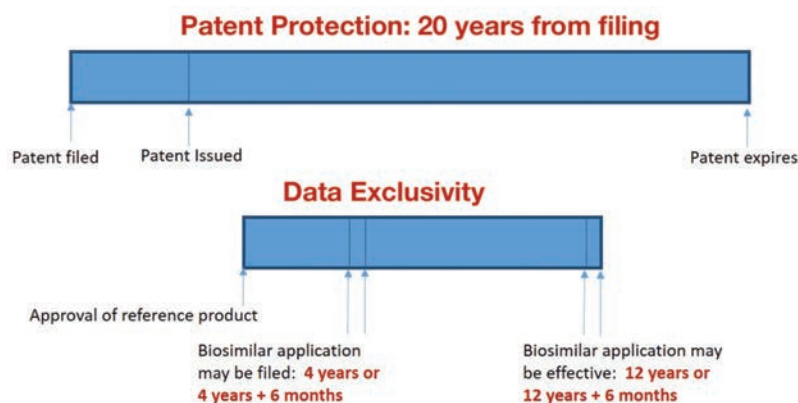
APPROVAL AND PATENT EXPIRY FOR COMMON BIOLOGICS



Until recently, in the United States a 12 year exclusivity period was provided for new biological products under the Biologics Price Competition and Innovation Act (BPCIA). This provision part of The Patient Protection and Affordable Care Act. Two entities make up this term of exclusivity: data exclusivity and market exclusivity. The law provided four years of data exclusivity for biologic drugs, while the remaining eight years function as market exclusivity. This is an important distinction because it means that after only four years the clinical trial data from original biopharmaceutical product is accessible and a developer may file an application under the Biologics Price Competition and Innovation Act (BPCIA) for a biosimilar, but such a biosimilar application would not be eligible for approval until the 12-year marketing exclusivity period has elapsed. Each exclusivity can be extended 6 months for pediatric applications.

These exclusivity protections are intended to encourage biologic research and development. Patents can be challenged in court, but exclusivity cannot.

DATA EXCLUSIVITY & PATENT PROTECTION:



Extended periods of data exclusivity would mean that there would be no access to clinical trial data from original biopharmaceutical products and without access to the originator data, biosimilar manufacturers cannot file their own regulatory applications. Repeating trials is too costly and would not be permitted because it would be considered unethical under the rules of the Declaration of Helsinki, a set of ethical principles regarding human experimentation and research.

There has been a great deal of recent debate regarding the exclusivity period for biologic products and when their biosimilar counterparts can make steps forward into the marketplace. In 2015 the period of exclusivity of biologic pharmaceuticals was a hot topic at the meeting of the Trans-Pacific Partnership (TPP), a free-trade agreement negotiated over eight years among a dozen Pacific Rim nations (United States, Japan, Brunei, Darussalam, Canada, Chile, Malaysia, Mexico, New Zealand, Peru, Singapore, Vietnam and Australia). The United States campaigned for 12 years of data exclusivity, which they felt would capture an appropriate balance between motivating future innovation and stimulation of research into new biological products while providing access to biosimilars in a timely manner. Alternatively, Australia and New Zealand argued that five years would be optimal, allowing for greater patient access to cheaper biosimilar medicines. In October 2015 it was announced that biologic drugs will be given a minimum of five years of data protection.

Biopharmaceutical companies continue to contend that developing biologic medicine is far more complex, expensive and time-consuming relative to chemically derived pharmaceuticals, and that this added complexity should warrant a greater period of data exclusivity for biologics, thus delaying approval of biosimilars.

There continues to be significant debate, both domestically and internationally, over how long biologics should be protected from competition.

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Chapter 7: What's in a Name?

Challenges in Naming Biosimilars

So what is in a name? And why is there so much debate about the naming of biosimilars? Shakespeare declared that a rose by any other name would smell as sweet, but the pharmaceutical world is a very different rose garden. When it comes to medications, a name means a great deal, affecting everything from how clinicians perceive the drug to how pharmacists dispense it. In the specific case of biosimilars, a drug's name can clearly signify whether or not it has met certain regulatory criteria and is officially considered "biosimilar." If the name doesn't communicate that to clinicians, biosimilars are less likely to be prescribed, limiting access to these lower-cost, safe and effective drugs. Or worse, confusion about biosimilar names could lead to prescribing errors.

In the US, the draft guidance from the FDA indicates that in order to differentiate biosimilars from their reference products, a suffix is to be added to the non-proprietary name of the drug. Keep in mind that biosimilars are approved by regulatory agencies to have similar clinical results as a brand name biologic drug. However, adding prefixes and suffixes to biologic products historically means that something is clinically different with a drug (example: pegfilgrastim is a clinically different, longer acting drug than filgrastim). Identical names may create a safety risk, as patients may not be aware that they are taking a similar version, not an identical version, of a branded product. Payors and biosimilar manufacturers prefer identical names so as to encourage interchangeability and therefore, substitutability at the pharmacy or prescription level. Branded companies argue that different names will ensure accurate medical records, manufacturer accountability, and appropriate use.

As more biosimilars enter the US marketplace, consider the challenges for physicians and pharmacists. A pharmacist goes to his computer to fill an order of "filgrastim" from the physician and sees that there are multiple versions listed. Given the history of biologic naming, it may not be surprising if he assumed that an added prefix or suffix means the drug has a substantially different clinical effect and would dispense the branded version of filgrastim, without considering if the physician may want the more cost effective biosimilar option. For these reasons, the FDA is proceeding with great care and caution as they move toward finalizing the naming requirements.

The naming of biosimilars represents another potential challenge for the manufacturers of the product, regulatory agencies, pharmacists, physicians, and payers, creating somewhat of a tug-of-war between the interests of each. Why does the name matter? Without unique identifiers for all biologics and biosimilars, accurate dispensing and correct identification of the brand, in case of adverse events, cannot be ensured.

For the sake of simplicity, most stakeholders would like to see biosimilars identified by a non-proprietary name corresponding to the originating branded biologic. However, this is not the most suitable choice because unlike conventional generic chemical drugs, biosimilars differ structurally from the branded biologics and the two must be easily distinguishable; therefore, they may not automatically be assigned the same generic name. Multiple biosimilars for each branded biologic agent may also be available, so it would not be appropriate for all of them to be known by the same name because each will have unique characteristics due to manufacturing considerations. Assigning all related biosimilars the same name would also confuse prescribing and dispensing of these agents and would complicate reimbursement and post-marketing tracking. This discernable difference is critical to minimizing patient and physician bias and how the interchangeability of different, but related, products may be interpreted.

The nomenclature (naming) standards for biosimilars have been a big part of regulatory policy development and implementation of pharmacovigilance strategies. Specifically, to ensure that any adverse events that occur after a drug has been approved, can be easily traced back to the manufacturer and matched to the specific product.

Adding to the complexity, there is currently no global consensus on naming methods for biosimilars. As we have seen in Chapter 4, different countries vary in their regulation and approval practices and associated requirements. As well, after approval the governing rules related to substitution and interchangeability of drugs, and who is authorized to make these decisions, also differs.

Naming of Small Molecule Drugs and Generics

Existing naming strategies for small molecule drugs have been well established and accepted. In 1953, in an effort to make communication related to pharmaceuticals and prescribing more standardized and precise, the World Health Organization (WHO) coordinated a naming system for small molecule or chemically synthesized pharmaceuticals referred to as International Non-proprietary Names (INN). INNs have been used as official generic and non-proprietary names associated with the drug or its active ingredient for decades. In the United States, generic names are approved through the US Adopted Names Council (USANC), which is sponsored by the American Medical Association (AMA), the United States Pharmacopeial Convention, and the American Pharmacists Association (APhA). USANC selects simple, informative, and unique generic names for drugs based on logical nomenclature classifications associated with pharmacological and/or chemical relationships. The brand name or trade name is developed by the company requesting approval for the drug and identifies it as the exclusive property of that company. When a drug is under patent or exclusivity protection, the company markets it under its brand name. When the period of protection expires (no longer protected by patent or exclusivity), the company may market its product under either the generic name or brand name. Other companies that file for approval to market the off-patent or off-exclusivity drug must use the same generic name but can create their own brand name. As a result, the same generic drug may be sold under either the generic name or one of many brand names.

As an example, brand name Arimidex (INN: anastrozole) is a drug manufactured by AstraZeneca and was approved for treatment of breast cancer after surgery, as well as for metastasis in both pre and post-menopausal women. In June 2010 the branded product, Arimidex, came off patent, opening the doors to other manufactures to submit generic versions for approval and marketing. By the end of that same month, the FDA had approved 11 generic versions of anastrozole, all with different brand names and varying price points.

Naming of Biosimilars is Different Than Generics

In October 2012, the WHO indicated that use of identical INNs for biosimilars was not appropriate and may lead to inadvertent switching between products. They added a recommendation that distinguishable names could be implemented by providing biosimilars with either a non-proprietary name from the reference product or by assigning a unique prefix or suffix to the root non-proprietary name of the reference product. At that time, WHO policy for assigning INNs to structurally related biologics (i.e., with identical amino acid sequences) followed two different approaches, depending on whether the biologic was glycosylated or not. Nonglycosylated biologics and biosimilars, which are considered to have posttranslational modifications that are highly similar to those of the originator product, receive the same INN. In contrast, glycosylated biologics and biosimilars, which are considered comparable but distinct from a previously approved product with the same amino acid sequence, would receive the root INN of the reference product plus a Greek letter suffix (spelled out in full) to indicate different glycosylation patterns. For example, the glycosylation of epoetin zeta biosimilars differ from that of the reference product, epoetin alfa. This naming system was voluntary and not mandated, therefore global variability in naming strategies exists.

We can look at the naming example of the first biosimilar to be approved in the United States, which does not align with the above recommendation. Zarxio is manufactured by Sandoz, Inc. and is the biosimilar to Amgen Inc.'s Neupogen, both are nonglycosylated biologics. The INN for Neupogen is filgrastim and the FDA designated a placeholder non-proprietary name for Zarxio as filgrastim-sndz. This "placeholder" provision for this product was because at the time of approval, March 6, 2015 the FDA had not yet issued draft guidance on how current and future biological products marketed in the United States should be named.

On August 31, 2015 the FDA announced its draft guidance, "Nonproprietary Naming of Biological Products," in which the agency articulates the need "for biological products licensed under the Public Health Service Act (PHS Act) to bear a non-proprietary name that includes an FDA-designated suffix." This means that the proper name of all biologics includes a core name and a designated suffix. For originator products, the core name would be the name adopted by the United States Adopted Name (USAN) Council for the drug substance when available. Related, biosimilar or interchangeable products would include the core name of the relevant, previously licensed product and a designated, 4-letter suffix attached by a hyphen. At the time of the release of this guidance document, the FDA also requested public feedback regarding whether an interchangeable biosimilar should be identified by the same suffix as its corresponding branded biologic. The FDA documents further states: "By differentiating biological products from one another that have not been determined by the FDA to be interchangeable, this naming convention is intended to help minimize inadvertent substitution. Inadvertent substitution may lead to unintended alternating or switching of biological products that have not been determined by FDA to be interchangeable. A naming convention that differentiates among biological products also could help facilitate pharmacovigilance for all biological products. By applying this naming convention to all biological products, this approach is intended to: (1) Encourage routine use of designated suffixes in ordering, prescribing, dispensing, and recordkeeping practices and (2) avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathways."

What does this new draft guidance all mean? Again we will use Zarxio as an example, currently also known as filgrastim-sndz. Specifically, the new non-proprietary name for Zarxio would be filgrastim-bflm and the new name for Neupogen would be filgrastim-jcwp. The FDA would require manufacturers to market products under these names—the name on the Neupogen packaging would change. The FDA was seeking input on this draft guidance until October 27, 2015.

The Therapeutic Goods Administration (TGA), the authority responsible for regulating medicines in Australia plan to add a second word comprising the prefix sim- followed by a fantasy single syllable to each biosimilar. The Japanese Accepted Name (JAN) for biosimilars uses the INN followed (in parentheses) by the name of the reference substance + BS1, BS2, etc.

As an increasing number of biosimilars are approved around the world, individual regulatory regions are starting to create their own non-proprietary nomenclature schemes for biosimilars. The variability of naming systems adopted by different countries is becoming increasingly apparent, adding a new level of confusion to product identification. In several places, a distinctive non-proprietary identifier is added to the INN. As an example, biosimilars of brand products Epogen, Eprex and Procrit (INN: epoetin alfa) have been approved in several countries. In Japan, the naming of the biosimilar of epoetin alfa has the code 'BS' added, making it 'epoetin alfa BS'. In Australia, 'epoetin alfa' was registered by the TGA as 'epoetin lambda'. In Europe there are three biosimilar erythropoietins available whose brand names are Binocrit, Epoetin alfa Hexal and Abseamed. The INN for all three of these biosimilar erythropoietins is 'epoetin alfa', same as the originator product.

Different standards for naming a biosimilar in each country may create further confusion for clinicians and patients across the globe, especially in the evolving globalization of medical practices.

Another example is the biosimilar for Neupogen (INN: filgrastim) identified as 'Filgrastim Hexal' in Europe; 'Tevagrastim Teva' (for Laboratório Teva) and 'Filgrastine Blau' (for Laboratório Blau Farmacêutica) in Brazil; and 'Filgrastim-sndz' in the United States (for a 'Sandoz' marketed product).

In other countries, a proprietary name alone is used, in South Korea, Celltrion's biosimilar of Roche's trastuzumab is called 'Herzuma'; and Celltrion's biosimilar of Johnson & Johnson's Remicade (infliximab) is branded as both 'Remsima' and, in Europe specifically, as 'Inflectra'.

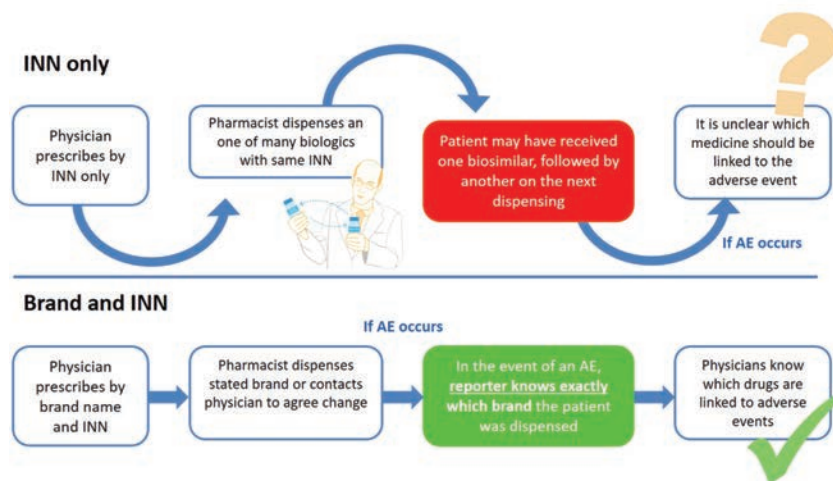
As we can see this can all be quite confusing, and few jurisdictions had adopted the 2012 WHO naming recommendations. This is why, since 2013, the WHO has been diligently working on a proposal to provide a unique identification code — called a Biological Qualifier (BQ) — for all biological medicines, including biosimilars. WHO states that a global unified naming system is central to ensuring the safe use of biosimilars — from the identification of the product in the clinical setting to its traceability after it reaches the patient. The proposed Biological Qualifier scheme was set out in a July 2014 draft, which was discussed at a closed meeting in Geneva on 13–15 April 2015 — the WHO's 60th consultation on INNs for pharmaceutical substances. Under the WHO naming proposal, the BQ would consist of a four-letter code suffix assigned at random, resulting in names such as 'filgrastim-bcdf' and 'filgrastim-wxyz'. The code would also be attached to the manufacturing site where the biosimilar is made. For instance, a company could have two different codes for the same biosimilar product manufactured at two different sites.

These randomly generated suffixes allow for 160,000 combinations of the four letters (excluding vowels), providing sufficient flexibility for the foreseeable future. The proposed BQ scheme would apply to all biologicals assigned an INN and it would be applied retrospectively. A database would be created to hold all the codes issued. It is important to note that the WHO emphasized that the BQ scheme would be universal but complementary to systems in place nationally, and its adoption by regulatory agencies would be voluntary. It would not be part of the INN, would be applicable to all biological substances, would uniquely identify the manufacturer or the manufacturing site, would be overseen by the WHO INN Expert Group and would be administered by the WHO INN Secretariat. The draft scheme highlighted that the BQ would be valuable for physicians and nursing staff, pharmacists, regulatory authorities, health authorities and patients.

Supporters of using the same INN for biosimilars note that different names would cause confusion among prescribers, which could negatively affect the substitution of interchangeable biosimilars, creating an artificial barrier to their adoption. The US Generic Pharmaceutical Association argues that, "Unique INNs would divorce the biosimilar from its shared regulatory history with the reference originator product on which its approval is fundamentally based, thereby reducing its safety. A biosimilar must have the same clinical pharmacology as the reference product, and by definition does not contain a new active ingredient. With a different INN, a prescribing physician may legitimately conclude that the active ingredients are different and so not recognise that the biosimilar and its related brand product have the same safety and efficacy history," it says. "As a result, physicians may prescribe two highly similar products to the same patient because they have different INNs, yet treat the same medical conditions, resulting in double dosing." It has been suggested that adopting National Drug Code (NDC) numbers or other product identifiers is sufficient to ensure accuracy for the purposes of substitution and postmarketing surveillance. This may sound like a simple solution, however, not all health systems use NDC identifiers and lot numbers, making it challenging to trace adverse events accurately.

Alternatively, proponents of using a unique INN for biosimilars explain that in order to reduce inappropriate or inadvertent product switching, as well as to clearly identify products for the purposes of substitution, pharmacovigilance, and patient surveillance, distinct names for each product are needed. However, using unique non-proprietary names for biosimilars may also have disadvantages, including confusion among prescribers about the comparability and

interchangeability of products, and potentially lead to prescribing and administration errors. When considering biosimilars for formulary inclusion, it is important for the review committee to consider how the names of biosimilar products will affect institutional computer systems used for tracking adverse events associated with a dispensed biologic or biosimilar. Using distinct names for biosimilars and the branded biologics is one of several ways pharmacists will be able to track these products; however, if the products share the same non-proprietary name it may be necessary to implement special tracking procedures. If a healthcare facility has access to bedside barcode scanning technology, some of these tracking concerns may be alleviated as details will be entered into the electronic record, but this is not available at all centers.



Without unique identifiers for all biologics and biosimilars, prescribing by brand name and INN supports accurate dispensing and correct identification of the brand in case of adverse events.

Survey Says...What Stakeholders are Saying About Naming, Recognizing and Reporting of Biosimilars

Tracking and traceability is a key safety concern when naming biologic and biosimilar products.

In Europe, a study was conducted to examine the traceability of approved biological medicines during the reporting of adverse events. Results revealed correct recognition of 96.2% of biosimilar medicines available in Europe, during adverse effect reporting. However, only 17%, or one in six physicians, still reported only the INN and only slightly over half reported both the INN and the brand name. Also, slightly more than one quarter of physicians never reported the batch number whereas only 40% always included the batch number in adverse event reports. Additionally, where patients are able to report adverse events directly, the study found that 40% of direct reports by patients did include the batch number of medicine, emphasizing the important role of patients in ensuring the traceability of biological medicines.

In 2014 an online survey of members of the Academy of Managed Care Pharmacy (AMCP), the APhA, and the American Society of Health-System Pharmacists (ASHP), asking participants their opinions about substitution of interchangeable biologic using different naming scenarios. The survey results indicated that 74.6% of pharmacists felt "confident" or "very confident" in substituting a biosimilar for a branded biologic if the products shared the same nonproprietary name. Interestingly, when presented with a scenario where the biosimilar and the branded biologic had different nonproprietary names, only 25.3% of participants indicated the same confidence level. These results showed that the naming strategy for biosimilars will indeed be a factor in substitution practices for interchangeable biosimilars.

In another survey, this time of 376 oncologists and practicing in the United States, results indicated that 75% of prescribers perceived products with the same INN as structurally identical, and that nearly 70% of prescribers interpreted a shared non-proprietary name to

mean that a patient could receive either product safely and expect the same results. These are interesting findings, because as we know, effective pharmacovigilance requires that all biologics within a product class must be distinguished from each other in order to facilitate accurate tracking of products and tracing of adverse events to the correct product manufacturer.

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Chapter 8: Economics of Biosimilars – the Promise of Lower Prices, but at What Cost?

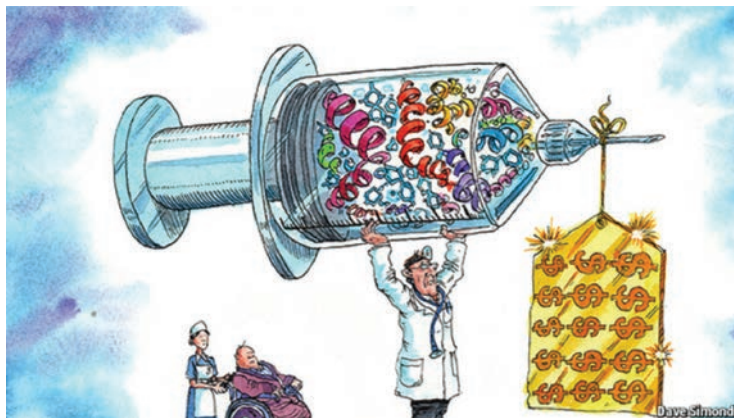
Ted is a 52-year-old man with non-Hodgkin's lymphoma. He does plan to undergo an autologous hematopoietic stem cell transplant (HSCT) and when discussing the associated risks, his oncologist warns that his white blood cells will become critically low as a result of high-dose chemotherapy. The low WBCs will place him at an increased risk for developing a possibly life-threatening infection. The oncologist will minimize Ted's risk of infection by giving him an injection of a granulocyte colony-stimulating factor; a glycoprotein to stimulate white blood cell production and decrease the length and severity of neutropenia.

Once the oncologist steps out of the room, the nurse arrives to provide additional information about the transplant and administration of the glycoprotein. Ted has heard that biosimilars have recently been approved in the US and wants to know if he might be receiving one. The nurse explains that the institution now prefers the biosimilar filgrastim product to the original trade name Neupogen. Ted wants to know if the institution's decision of preference was made on cost alone? He understands that the cost of his cancer treatment is high and grateful that he has health insurance, but he is concerned that the biosimilar treatment will not be as effective as the original product in reducing his risk of a life-threatening infection. The nurse assures Ted that the hospital's decision to use biosimilars is based on scientific evidence and that in order for the treatment to be approved by the FDA, they would have reviewed sufficient data to support the role of a biosimilar form of Neupogen in the prophylaxis of complications related to neutropenia caused by chemotherapy.

There is no doubt that biological medicines have revolutionised the management of a number of diseases and offer treatment for some conditions that were previously untreatable. The key barrier to access for patients globally continues to be the high costs associated with these treatments.

Let's look at the treatment of melanoma as an example. As we know, melanoma, the most aggressive type of skin cancer, is more likely to spread to other parts of the body than other forms of skin cancer. The number of melanoma patients has been on the rise over the past several decades, according to the National Cancer Institute, with an estimated 73,870 new cases and 9,940 associated deaths in 2015. In stage III melanoma, the cancer has infiltrated one or more lymph nodes and treatment generally includes surgery to remove the melanoma skin lesions and the nearby lymph nodes. In 2011 ipilimumab (brand name Yervoy), a monoclonal antibody that blocks a molecule known as CTLA-4 (cytotoxic T-lymphocyte antigen) was approved to treat late-stage melanoma that could not be removed by surgery. Research has shown that CTLA-4 may play a role in slowing down or turning off the body's immune system, and affects its ability to fight off cancerous cells. Yervoy may work by allowing the body's immune system to recognize, target and attack cells in melanoma tumors. In 2015 its approved use was expanded, as adjuvant (enhancing the existing medical regimen, such as surgery) therapy for patients with stage III melanoma. The unfortunate part of medical breakthroughs like this is that the associated costs are likely out of reach for the average American. The price for one injection is \$30,000 (or \$120,000 for a full course of treatment). This hefty price tag is not unique to Yervoy, other immunotherapies carry similar costs to treatment.

You may wonder, “Why are biologics are so expensive?” well, the high costs, including development, materials and manufacturing costs are significantly higher than traditional small molecule chemical medicines. It is estimated that in order for a company to develop, manufacture, conduct research studies and move a biologic product through to the regulatory approval process, it will cost a company \$800 million to \$2.5 billion. As well, companies hope that a drug approved for use can help them recoup some of the costs associated with drug development failures that didn’t make it through all the regulatory approvals and were shelved after years of development. Less than 12% of new therapies that begin clinical experimentation actually get approved and marketed for use. If we look at the melanoma example, seven new treatments were approved over the past 15 years, while 96 were abandoned. Similarly, in lung cancer treatment, while 10 products were successfully developed, 167 did not cross the finish line. Perhaps recovering the costs of a company’s less stellar ventures is why costs of successful treatments continue to rise.



Source: Dave Simons

A Mayo Clinic study looked at the costs associated with cancer treatment over the past decade and found that in 2000, cancer drug prices were between \$5,000 and \$10,000 for a year of treatment. In 2012 the costs skyrocketed to more than \$100,000. As an example, in 2001 when Gleevec revolutionized chronic myeloid leukemia treatment, increasing five-year survival rates from 30% to 90%, its annual cost was approximately \$30,000. A decade and a half later of high profitability, the costs for this same treatment have ballooned to \$132,000 annually. Sadly, the average American household income also dropped by 8% during that same time period. Fortunate patients are somewhat protected from these high costs by their insurers, but many, such as those on Medicare, are required to come up with 20% copays, which translates to \$20,000 annually. An unmanageable cost for so many that can lead to tough choices and risky behavior. It has been reported that 20% of patients will chose to miss a dose, at least once a month, and 14% will postpone having their prescriptions filled in order to attempt to manage costs.

The financial burden of cancer care has been a topic of recent research. In 2013 the Fred Hutchinson Cancer Research Center in Seattle released the findings of a study that showed that someone who has received a cancer diagnosis is 2.5 times more likely to be forced into filing for bankruptcy. In 2014 the Cancer Support Community surveyed 7,000 cancer patients to find that nearly half were plagued with financial anxiety and a third of respondents had drained their savings or retirement savings in order to cover the costs of their care.

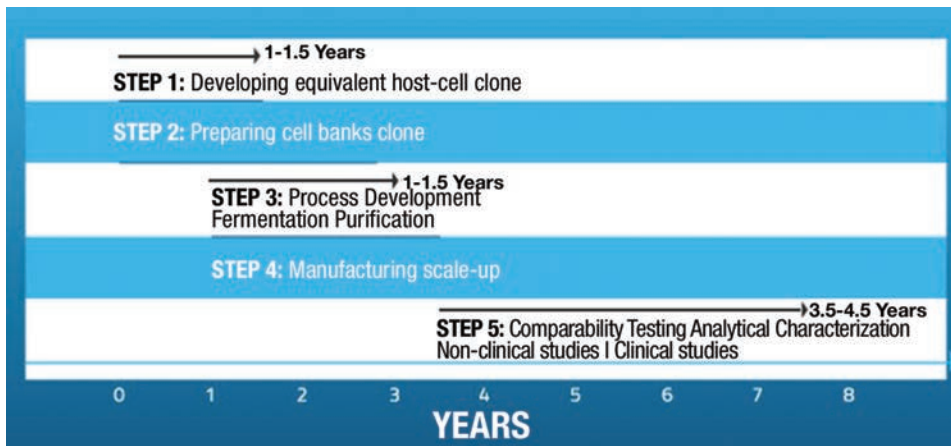
Can Biosimilars Rescue Patients from High Costs?

A great deal of motivation for the use of biosimilars is directed toward improving sustainable access to biological therapies in a cost-efficient manner, whereby managing healthcare costs. This is tremendously important in oncology when we consider that over the decade between 1998 and 2008 the costs associated with cancer drugs in the US increased by fourfold, with the majority of this increase being attributable to high-cost biologics.

Biosimilar products do not have all of the costs associated with the rigorous testing and approval as their reference products had, which is why The US Congressional Budget Office has estimated that biosimilars will cost 20–40% less than the original reference products. Although the US is just beginning to see biosimilars entering the market, the European Union has reported 10-35% discounts for biosimilar treatments, compared to the reference products. While any reduction in cost is positive, it certainly is not comparable to the typical 70-80%

discount for small-molecule generic drugs. This is because the development and manufacturing process is much more complex for biosimilars than generic drugs. Biosimilar development takes between five and nine years, costing \$75-250 million, as compared to generics which typically take approximately three years and \$2-3 million.

If we look at Zarxio, our first biosimilar to hit the US market, in September 2015, Novartis reported that the US wholesale list price for a 300 microgram syringe is \$275.66, with the 480 mcg version costing \$438.98. Neupogen, the reference product costs \$324.30 and \$516.45 for the same syringe formulations, according to Amgen. This 15% discount is similar to the price difference when Zarxio was launched in Europe in 2009. Since then, the price gap has widened to approximately 20-30%.



Adapted from *Biosimilars Handbook*, European Generic medicines Association, Second edition, 2011.

The European Commission has also noted that as biosimilars have entered the marketplace, they have observed enhanced price competition from the original biologics, leading to cost savings for patients, healthcare systems and payers, potentially improving patient access to these treatments.

“Biosimilars will provide access to important therapies for patients who need them,” said FDA Commissioner Margaret A. Hamburg, MD. “Patients and the health care community can be confident that biosimilar products approved by the FDA meet the agency’s rigorous safety, efficacy and quality standards.”

A biosimilar therapies emerge as a potential treatment option for cancer patients, it will be critical for oncologists, institutions, and payers to evaluate the potential cost savings by incorporating biosimilars into clinical practice. Particularly being mindful of any differences that exist between the biosimilar and its reference product in the context of manufacturer patient-assistance programs, out-of-pocket costs to the patient (co-pay or co-insurance), and institutional costs associated with patient education and support. Availability of lower cost biosimilar medicines creates the potential for funds that would have been previously allocated to higher cost drugs to be accessible within healthcare systems and reallocated to other areas in need. A 2013 report from prescription drug benefit management company, Express Scripts, estimates “the United States would save \$250 billion between 2014 and 2024 if the 11 likeliest biosimilars are approved.” This estimate is much higher than the review of literature regarding biosimilar cost saving estimates, published by the Rand Corporation in 2014 which stated, “We estimated the cost savings potential of biosimilars to be \$44.2 billion over ten years using available information and a survey of the literature.”

It is also important to recognize that biosimilars are not going to be all about cost savings. It is likely that in order to implement biosimilars into an institution or care facility, there may be costs associated with modifications to existing technology systems to facilitate accurate tracking, tracing and differentiating biologics and biosimilar to ensure accurate recordkeeping and prescriber notifications in the case of changes or substitutions.

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Chapter 9: Barriers to Acceptance into Clinical Practice

Because the use of biosimilars in the US is just in its infancy, many physicians are still forming their opinions, pondering the advantages and voicing concerns. In December 2015, Dr. John Sweetenham, the executive medical director at Huntsman Cancer Institute and professor in the Department of Medicine, Division of Hematologic Oncology at the University of Utah wrote a very timely article in HemOnc Today. Dr. Sweetenham expresses his opinions regarding the use of biosimilars in practice and how his sentiments have shifted from being a topic that wasn't really on his radar screen to skepticism, to now, "my opinion has matured into uncertainty as I ponder value in health care, the potential societal benefits of the agents, and the possible impact on research and innovation." He stresses that, "as oncologists, we are not likely to have confidence in a product that has not been extensively evaluated against the standard of care in a randomized clinical trial. For our patients, the stakes are too high to be messing around with a cheap "knock-off" drug of uncertain efficacy." Dr. Sweetenham advocates for his patients, wondering if the millions of dollars developing drugs that are no better than existing compounds, "might be better spent on research into new targets and new anticancer drugs rather than offering patients the status quo." He feels that biosimilars may offer potential societal benefits, by driving down the cost of these agents through competition, "then health care systems, insurance companies and — most importantly — patients stand to win." He has observed cancer care in India where seven versions of rituximab are currently available, leading to improved drug access in a resource-limited health care system which undoubtedly has saved lives. He concludes, "Overall, my mind has been opened to the possibility that biosimilars will benefit our patients in the short term, although the long term is less certain. What's for sure is that they are not going away. We will need to be vigilant about the risks to innovation, and to how use of these drugs is driven by payers, but we should keep an open mind for now."

Biologics have become an essential part of cancer treatment and supportive care; and therefore, oncology practices will be greatly affected as biosimilars make their way into the US market. The thought of a less expensive treatment that can deliver safe and effective results is quite promising, but not without some barriers and challenges to acceptance. Physicians, professional societies, practice guidelines and other healthcare providers and patients will be key in determining how biosimilars are integrated into clinical practice.

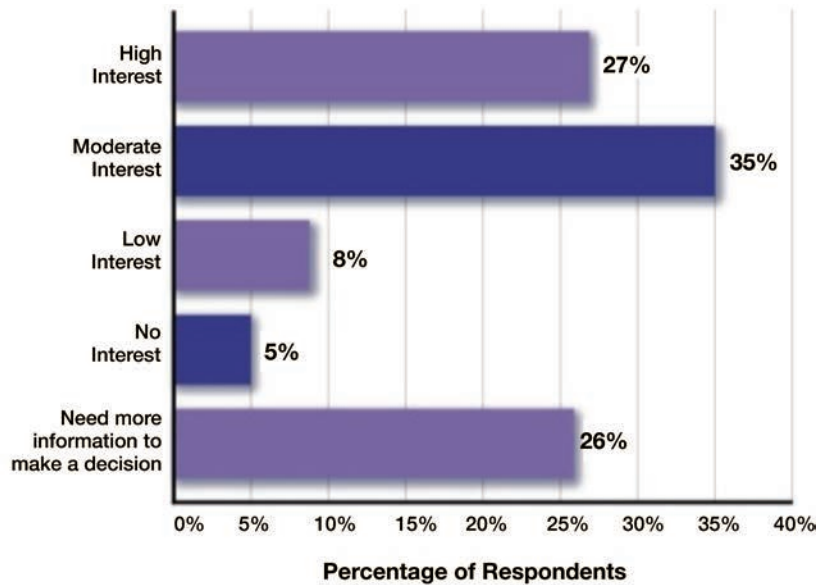
Cost should not be the primary driver for decision making in choosing the right biologic medicine for a patient – science and patient safety should lead decisions.

Physicians and other healthcare professionals need to fully understand biosimilar products in order to make informed decisions for their patients. In 2013, a Continuing Medical Education (CME) survey asked more than 400 medical professionals, including oncologists about their knowledge of biosimilars. The majority of respondents had a 'poor to fair' understanding of the steps that a biosimilar product has to go through to receive regulatory approval, specifically regarding appropriate clinical trial design and study endpoints. Most respondents did feel that biosimilar education was 'important or very important' to their clinical practice, supporting the need for access to information regarding the use of biosimilars, efficacy and safety data, as well as immunogenicity data.

In another survey, oncologists practicing in Italy were asked about the use of erythropoiesis-stimulating agents for anemia induced by chemotherapy. 45% of respondents indicated that they anticipated using biosimilars in place of the original reference product and more than half

(54%) stated that reduced costs were the primary motivating factor and 26% felt that the use of biosimilars for chemotherapy-induced anemia was scientifically supported. Alternatively, for the 55% that did not feel that biosimilars were an adequate replacement for the original biologic, 42% specified that there was a lack of clinical studies to support their use.

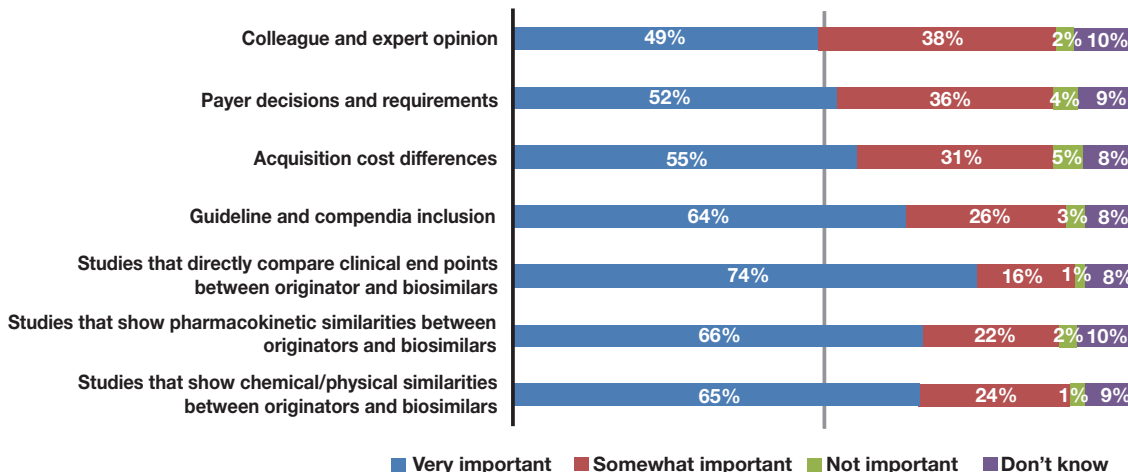
In 2011, the National Comprehensive Cancer Network® (NCCN®) asked US physicians, nurses and pharmacists involved in oncology care what their overall interest was in using biosimilars. At the time, there were no biosimilars approved for use in the US, but 35% reported that their interest was 'moderate', while 27% reported a 'high' level of interest.



Zelenetz AD, Ahmed I, Braud EL, et al. NCCN Biosimilars White Paper: Regulatory, Scientific, and Patient Safety Perspectives. *J Natl Compr Canc Netw* 2011;9(Suppl 4):S1–S22.

Central to the issue of acceptance is the education of physicians, other health care practitioners, patients, and payers on biosimilars and the regulatory issues surrounding them. That NCCN survey mentioned above also suggested that there may be some limitations in the overall knowledge of biosimilars in the medical community. About a quarter of respondents reported that they felt they needed additional information about biosimilars before they would be comfortable making decisions about their future use. Of the types of information listed in the survey, a majority of respondents listed them all as 'very important' to their decision-making process.

CONSIDERATIONS IN DECISION-MAKING PROCESS INFORMATION BIOSIMILAR USE: NCCN SURVEY RESULTS



Even though patients may be more likely to opt for a potentially lower priced treatment option, their oncologist may be reluctant to prescribe a biosimilar for the treatment of their cancer without having access to the knowledge and data supporting the use of that particular product for that specific indication.

Some other key considerations, specific to oncology practice that have been outlined as barriers to biosimilar acceptance into clinical practice include: Interchangeability and substitution regulations; Extrapolation of indications (meaning that if the reference product is safe and effective for a new type of tumor, is the biosimilar safe and effective as well?); ongoing safety monitoring (pharmacovigilance) after approval; the naming of biosimilars; and the economic implications.

Another important barrier to implementing a biosimilar into a patient's treatment plan is that a person prescribed a biosimilar may have a different response than if they had been prescribed the originator biologic - and vice versa - because the two are not identical. This switching between non-identical drugs is thought to potentially increase the risk of an immune response against the drug itself. This is why physicians should be well-informed on each product's benefit/risk profile and how it evolves over time. Physicians, in consultation with their patients, should retain the decision-making role in the choice of which drug is most appropriate for their patient and the condition being treated.

Key questions that health care providers want to know about biosimilar products are:

- Is there clinical evidence that demonstrates biosimilarity in purity, safety and potency between the biosimilar and the reference product in the condition being treated?
- Is a similar mechanism of action expected for the condition being treated?
- Is the dose response relationship the same between products?
- Can similar pharmacokinetics be expected in a particular patient population?
- Are there any anticipated differences in toxicity or immunogenicity between products?
- What are the factors that might influence safety and efficacy in the patient population? (comorbidities or concomitant medications)
- If my patient is already using a biologic, what differences can I anticipate using the biosimilar?

Reliability of the Biosimilar Supply Chain

Biosimilars are new to the US market, but physicians and other healthcare stakeholders have concerns about the reliability of the supply chain, moving forward. Using generic drugs as an example from previous experience, physicians have found that even though the generic alternatives can reduce drug costs for their patients, disruptions to clinical supply have become a common, and unfortunate occurrence in many oncology practices. These previous shortages of medication, needed for cancer treatment, have led to rationing of drugs, delay of critical treatments, switching of therapies during a course of treatment or substitution of drugs that are less efficacious or more expensive. Often, drug shortages have been attributable to issues in the manufacturing process, leading to inadequate quality of the final product. This has become such a prominent and ongoing concern that it is being addressed by professional oncology organizations and the FDA.

Although having an alternative to a biologic drug, in the form of a biosimilar could also reduce drug costs for patients, similar disruptions to the available clinical supply are a great concern for oncologists. The robustness of the manufacturer's supply chain is an important consideration for oncologists and medical facilities when evaluating biosimilars. Patients must be able to receive their scheduled doses of the planned treatment consistently. Oncologists and other key stakeholders have stressed that examining a manufacturer's history of shortages or recalls

related to quality concerns will be important, as well as evaluating a company's capability to maintain consistent, reliable, high-quality supply of their biosimilar products. It has been recommended that manufacturers demonstrate a proactive strategy by investing heavily in their inventory and infrastructure to reduce the risk of product shortages or have an efficient plan for recovery in the event a shortage occurs.

Amgen, the company that manufactures the first approved biosimilar in the US is aware of the concerns of stakeholders and has worked to develop a multifaceted approach to help prevent drug shortages. In order to reduce the risk of product manufacturing issues and ensure a reliable supply of consistent quality, they have invested in inventory management strategies at multiple points in the supply chain to mitigate potential risks of disruptions to supply (e.g., natural disasters). Additionally, they maintain appropriate levels of raw materials by diversifying suppliers of sourced raw materials and storing high-risk raw materials in multiple geographical locations to safeguard their availability. Amgen also states that by managing relationships with their suppliers, they ensure that raw materials are of the highest quality, reprocessing is minimized and the risk of potential manufacturing issues is reduced.

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Chapter 10: What is on the Horizon? Growing Availability and the Future of Biosimilars

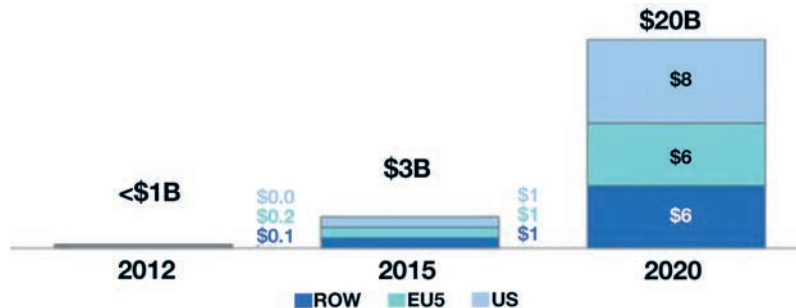
The use of biosimilars is growing around the world, providing greater access to medicines for many patients. Although the US has lagged behind other countries in their biosimilar development programs, it appears that the process is now moving ahead at full speed. As of July 31, 2015, the FDA had 57 proposed biosimilar products (to 16 different reference products) enrolled in the Biosimilar Product Development (BPD) Program. The number of sponsors in the BPD Program is not absolutely reflective of the overall number of industry programs underway, as a sponsor may be in the early stages of interacting with FDA and not yet enrolled in the BPD Program. Sponsors of an additional 27 proposed biosimilar products have had a Biosimilar Initial Advisory meeting with FDA, but have not joined the BPD program to pursue the development of these products. This means that more than 80 biosimilar products are working toward crossing the approval finish line. Keep in mind that Europe just reached its 10 year anniversary of biosimilar approval, and as of December 2015 has approved 19 biosimilars, corresponding to 6 different reference drugs, in six categories of biologics: epoetins, filgrastims, follitropins, growth hormones, insulins, and monoclonal antibodies.

The FDA is also making strides in building stakeholder confidence, by actively engaging key stakeholders throughout the development process by continuing to hold both public and stakeholder meetings. The FDA also is undertaking a multi-phase plan for communicating with stakeholders and educating them about biosimilars. The first phase of the communication plan is to lay a solid foundation with understandable definitions and descriptions that health care professionals and consumers can easily understand and adopt. To help guide message development, FDA has a contract to conduct a focus group study of prescriber and pharmacist knowledge of biosimilar biological products. FDA also has a contract for Web-based training programs, which includes a biosimilar course to educate health care professionals (physicians, nurses, pharmacists, nurse practitioners and physician assistants) nationwide. FDA plans to communicate information in various formats to consumers as more biosimilar products are approved and enter the marketplace and continue outreach activities, including interacting with physicians and pharmacists and educating consumers and patients, well into the future.

Over the past 30 years, there has been tremendous growth and development of biologic agents in the pharmaceutical industry. The US and European markets for biologic agents presently account for approximately \$60 billion in annual sales, and rapid expansion of the number of marketed biologics is anticipated. Because of the success of biologics, biosimilar development represents a large profit potential for pharmaceutical manufacturers. Consumers and policy makers also view appropriate market introduction of biosimilars as high priority because of the prospect of reduced medical costs.

A number of biologics with very high annual sales will lose exclusivity protection in the next few years. These include Rituxan (rituximab, an anti-inflammatory and chemotherapeutic agent), Enbrel (etanercept, used for rheumatoid arthritis), and Remicade (infliximab). It is predicted that as patents and exclusivity periods expire, the development of biosimilar medicines for the treatment of cancer, diabetes, rheumatoid arthritis and multiple sclerosis will be seen. It is predicted that the monoclonal antibodies (mABs) will comprise a large proportion of the biosimilars market.

BIOSIMILARS MARKETPLACE, GROSS SALES



Production and sales of biosimilars is estimated to reach \$20 billion in annual business by 2020

PROJECTED GLOBAL ANNUAL SALES OF BIOSIMILARS



Source: Drug Discovery & Development, 2015

As more biosimilar medicines become available, there will be opportunities for manufacturers to improve packaging and administration methods for these medicines. For example, some biosimilars in Europe are currently being produced with a 'Patient Support Kit' which allows patients to self-administer the medicine at home. This could allow for biosimilar medicines to be used in primary care settings or in the home, instead of hospital settings, and could improve adherence to medication by improving access. Having said that, Blue Cross Blue Shield of North Carolina, researched how to improve adherence for biologicals by developing patient-centred interventions and according to Dr Marissa Blum of Temple University, Philadelphia, in many ways, adherence boils down to the individual patient-provider relationship. That said, due to the specific storage and handling requirements of most biologic drugs, administration outside a controlled hospital setting could raise safety concerns and monitoring challenges.

We can look at the European experience with the biosimilar, Omnitrope, which was the first biosimilar approved there in 2006. Omnitrope initially experienced minimal uptake by the healthcare community and while the fragmented marketplace appears to have been a key factor, much of the blame can also be attributed to the delivery device. In the first Omnitrope delivery system, the multi-step mixing of the Omnitrope and measuring of the dosage were two phases of the process that were much more complex than the original systems. This discouraged uptake and patient adherence. The manufacturer subsequently initiated a switch from a 'lyophilised powder form in a vial', to liquid cartridges in injector pens of varying strengths. The new systems represented increased convenience for patients because 'the

liquid is already dissolved in a ready-to-use cartridge and can be loaded into the pen for injection' and the manufacturer experienced increased sales. Executives have claimed that the new device represents a 'commitment to meeting the needs of patients through providing more convenient delivery systems', as well as its commitment to a fundamental business strategy of 'focus on difficult-to-make products that provide added patient benefits'

Biosuperiors

Efforts are already underway to go beyond "similar" and develop a new class of follow-on biologics named "biobetters" or "biosuperiors", which go beyond mimicking the original biologic to provide improvements to it through changes in chemistry, alteration in the formulation, and innovative delivery.

These are products similar to the original approved biologics, but with some measurable superiority such as extended therapeutic effect time or a reduced adverse event profile. Current biosimilar products are being developed and approved via the traditional 301(a) BLA pathway for biologics and are required to demonstrate efficacy and safety without the necessity of comparability studies designed to demonstrate their similarity to the originator molecule, thus relieving the biosimilar from conducting large Phase III comparative trials. Of course, the efficacy of the biosuperior product has to generate efficacy and safety data demonstrating a benefit/risk ratio of the same approximate magnitude as the innovator product, but not in a head-to-head comparison. The biosuperior developer will be measured against the results obtained by the innovator in their current package insert. Consequently, the work required for approval of a biosuperior would more closely resemble the 505(b)(2) New Drug Approval (NDA) regulatory pathway for "improved" approved drugs leveraging FDA's knowledge of previously approved innovator products as opposed to the 505(j) NDA pathway for generic drugs with its expectations of interchangeability.

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Chapter 11: What Patients Need to Know About Biosimilars

Frequently Asked Questions about Biologics and Biosimilars

Q. What is a biologic?

A. Biologics are medicinal products created using biologic processes in living cells. The more common small molecule drugs, typically delivered in oral form, are chemically synthesized. Biologics are complex, large molecule drugs manufactured using live cells and are generally administered as an injectable. Biologics provide new treatment options for serious illnesses, such as cancer, multiple sclerosis, and rheumatoid arthritis, and have enabled treatment where no effective therapies were previously available.

Q. What is a biosimilar?

A. When the period of patent protection expires on a biologic drug, other manufacturers may market copies of the compound. To be approved for sale, a biosimilar must demonstrate that it is a “similar biological medicinal product” to an already approved biologic drug, known as the originator drug or reference drug. The determination of “similarity” is made by the FDA on a product-by-product basis.

Q. Why are biosimilars not considered generic copies of the original biologic drug?

A. When the patent has expired on a small-molecule drug, other companies may make generic copies using the same drug formula. A generic drug is made from the same ingredients and has the same chemical structure as the original drug. To be approved, generics do not need to have undergone clinical trials (testing in patients to demonstrate efficacy and safety). The generic only needs to show that the active ingredient is available to the body at the same rate and to the same extent as it is with the original drug. A generic is generally considered to be bioequivalent (works in the body in the same way) as the original drug.

A biosimilar is NOT a generic copy of the original biologic. It is not considered to be bioequivalent. There are several reasons for this. A biologic drug is much bigger and more complex than a small-molecule drug. The manufacturing process for biologics is so complex that it is virtually impossible for a biosimilar manufacturer to generate an identical medicine to the originator biologic.

Q. How do biologic and biosimilar drugs work?

A. Chemical drugs generally treat symptoms of disease (for example, Aspirin for pain) while biologic drugs target the underlying cause. For example, some biologics replace proteins that are missing or not functional. Examples are insulin for diabetes, replacement factor for growth hormone deficiency, clotting factor for hemophilia and replacement proteins for rare lysosomal storage disorders. Some biologics are antibodies that target very specific disease-causing cells, such as those causing rheumatoid arthritis and some types of cancer. Finally, a bioengineered interferon can help the body’s own immune system work more effectively against a number of diseases, including cancer, hepatitis B and C, and multiple sclerosis.

Q. How are biologic and biosimilar drugs made?

A. Biologic drugs are structurally much larger and more complex than chemical drugs. Biologic drugs are made from cloned (genetically identical) copies of a master cell. The process starts by isolating the “genetic sequence” of DNA code responsible for the desired protein (factor, antibody, cytokine or other biological substance), which is the active ingredient in the biologic drug. This gene is inserted into a host cell, usually from a hamster or mouse. The cell produces

the desired protein from the genetic code, and this cell is placed into a culture where it multiplies. These cells are then transferred to large vats where they are processed and monitored at exacting conditions until the desired quantity of protein has been produced. The protein is then extracted from the cellular culture and purified and stabilized.

Q. What are the benefits of biologic or biosimilar drugs? Why might a patient be prescribed a biologic or a biosimilar?

A. Biologics are targeted to work in highly specific ways, so they are not only potentially more effective against the disease but also lead to fewer side effects. For example, chemotherapy (chemical drug) works by targeting actively dividing cells but because its action is “nonspecific”, chemotherapy interferes with normally dividing cells as well as cancerous ones. Biologic drugs, such as monoclonal antibodies, regulate the function of specific, defective cells that cause cancer growth without interfering with normal cells.

Q. What are the risks related to biologic or biosimilar drugs? What should patients be aware of when taking a biologic?

A. Because proteins are digested, most cannot be taken orally. Biologic drugs are typically injected into a vein or infused under the skin. Patients typically experience some reactions, such as redness, swelling or soreness, at the site of injection. These may vary in severity and frequency.

Because biologic drugs are larger and more complex than chemical drugs, they are also more likely to be recognized by the body as “foreign” and cause an “immune reaction.” Often, these reactions are mild and will subside over time. However, a very rare but serious reaction may occur.

Q. How can patients be sure that their biologic and biosimilar drug therapy is safe and effective?

A. All biologic drugs are reviewed for safety and efficacy by the FDA Health Canada before they can be sold. Any and all adverse reactions to a medicine should be reported to the manufacturer and the FDA. In some cases, patients may be treated for side effects and remain on the biologic drug; in some cases, the reactions may be serious enough to discontinue treatment, either temporarily or permanently. In all cases, the decision should be made by the physician in consultation with the patient based on the risks, benefits and alternatives.

Q. What factors should be considered in deciding between a biosimilar and the original biologic?

A. A biosimilar receives regulatory approval based on clinical and nonclinical similarity to the original (reference) drug. However, a biosimilar is not an exact copy of the original biologic drug, so the decision to take a biosimilar or the original biologic should be made by prescriber and patient based on individualized factors.

These factors may include cause, status, and responsiveness of the disease as well as the person’s perception of tolerability, manageability of the therapy, and impact on functioning and quality of life.

A biologic may cause an immune reaction to the active ingredient, to a stabilizer or another ingredient, or to an impurity from the manufacturing process. The safety profile of the original drug, including immunogenicity, may not extend to the biosimilar. Even minor changes in the process can lead to significant changes in the final product, and this may alter the risk of immunogenicity of the biosimilar relative to the original biologic.

Q. Are biosimilars cheaper than their biologic originators?

A. With only one biosimilar launched in the US, it is difficult to speculate how biosimilar companies will price their products. Having said that, it is estimated that the public will see a 10-15% lower costs. Because the production of a biosimilar is much more complicated than a small-molecule generic and therefore the development costs are higher, it is unlikely similar cost savings as those seen with generics will be found.

As many original biologics are beginning to reach the end of their exclusivity period, biosimilar manufacturers are using the opportunity to develop highly similar versions of the original authorised biologics. There is an opportunity for these biosimilars to be available at a lower cost than the original medicines, possibly making them more widely accessible to patients and offering more treatment options to physicians.

However, in common with the introduction of all new medicines, biosimilars raise a number of questions and concerns for patients, ranging from the approval process to safety and risk. Patients can only make informed decisions and choices about their treatments if they have access to reliable information and facts.

Availability of Clinical Study Data

If the reference biologic product has been authorized for use in the US for several years, and its clinical benefit has been established, then some of the research studies that were conducted with the reference biologic may not need to be reproduced for the biosimilar. Physicians and patients have commented that this has allowed approval of biosimilars after only very short or limited trials without sufficient time to consider any longer term effects of the medicine. There is added concern when extrapolation of indications is permitted, meaning that comparability studies in the context of one disease can be transferred to other indications without having to carry out any additional studies before approval. Patients wish to know what level of risk this presents to them and at the current time, this is unknown.

Lack of Global Regulation

It is becoming more common and easier for patients to travel to other countries to seek medical treatment options that may not be available where they live. Even though the WHO published its Guidelines on Evaluation of Similar Biotherapeutic Products in 2010 in an effort to provide globally acceptable principles to approve biosimilars that would assure quality, safety and efficacy, these principles are not firmly in place. Therefore, the possibility of cross-border availability and access of biosimilars from countries with differing approval regimes should also spark patients' concerns.

Similarity and Variability

Despite the approval of a biosimilar, due to the complexity of manufacturing and development, it will still have some degree of variability when compared to the original reference product. Patients must consider whether this variability might carry additional risk. Will biosimilars increase immunogenicity? Will side effects be the same as the reference biologic?

Switching, Interchangeability and Substitution

Although switching, interchangeability and substitution have not yet surfaced as an issue in the US, due to the limited biosimilar market, patients must still understand the risks associated with changing medications.

Many patients consider that leaving open the possibility of switching (transitioning between the reference product and the biosimilar) without the consent of the patient, interchangeability (going back and forth between the reference product and the biosimilar with the expectation of achieving the same outcome) without the knowledge/consent of the patient, and substitution (the practice of dispensing one medicine instead of another equivalent) without the knowledge of the prescribing physician and the patient, would introduce unacceptable uncertainties into that decision-making process. The FDA makes regulation on whether a biosimilar should be used interchangeably with its reference medicine, but substitution policies vary between states.

Decisions Based on Cost Alone

It is the expectation that that biosimilars will be introduced to the market at a lower price than their original reference products. Price is determined by many factors, such as market trends, competition between reference products that treat the same disease or condition and the biosimilar manufacturers. This has led to patients' anxiety that the availability of lower-priced biosimilars may increase pressure on clinicians, by health providers and insurers, to prescribe the newer alternative on the basis of cost alone.

Although the economic pressures on health care services are a very real issue, patients need to fully understand the treatment they will be receiving, beyond the costs savings. Decisions about prescribing biosimilars should be made on a clinical basis and not solely on financial grounds.

People should be fully aware of the medications that they are taking and have access to the information they need, in lay terminology, to make fully informed decisions about whether to take a biologic or biosimilar. They have to be able to assess risk against benefit accurately, and they need the tools to be able to discuss the pros and cons with their healthcare team.

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Key Summary Points

- Biologics are large, complex molecules manufactured from living organisms. Cell lines are programmed to produce a specific therapeutic substance (a "biosimilar") with a goal of replicating the safety and efficacy of an existing "reference" biologic drug.
- Biosimilars require a 2-step approval process by the FDA: the first step is to show "similarity" in safety and efficacy, and the second step is to show "interchangeability" with the reference drug.
- Biosimilars are approved for specific treatment indications, but the FDA may allow extrapolation to other disease states, depending on clinical evidence submitted.
- State laws permitting interchange at the pharmacy will likely have strict rules about record keeping and communication between prescriber and patient. More than half of states have yet to pass rules regarding substitution.
- The primary safety concern of patient advocate groups is that immunogenicity, or immune response, for any one patient, will differ unpredictably for different biosimilars for the same reference drug.
- Expected savings to health care systems will depend on how quickly prices change in response to competition, and how many biosimilars are produced for any one reference drug.

How Can Advocates Use This Information?

As advocates, it is important for us to understand this basic information about biosimilar medications, because of the growing role they are playing in cancer treatment. Even though biosimilars may provide the opportunity to improve patient outcomes by offering increased affordability and access, it is important to understand the similarities and differences between these products and their reference products, as well as the implications of these differences. Biosimilars extend therapeutic options, but do not create new therapies.

By gaining a working knowledge of biosimilars we will be able to communicate more easily with physicians and researchers and better understand future developments and perspectives. As well, we can translate our knowledge into messages that patients and their families can more easily understand.

“Biosimilars are likely to create greater competition in the medical marketplace,” says Leah Christl, Ph.D., Associate Director for Therapeutic Biologics at the US FDA. “This could not only increase treatment options for patients, but also lead to less expensive alternatives to comparable products. With an increasing number of biosimilars on the market, consumers may expect to get equally safe and effective treatment, but at lower costs.”

Patient organizations have identified some of the important issues regarding biosimilar medicines:

- Safety: (side effects, reliability, regulation) includes a broad range of issues from how biosimilars are defined and named, to their ability to cause immune reactions, regulation and pharmacovigilance
- patient information and education regarding biosimilar medicines
- switching between biosimilar medicine and reference product (prescription transparency)
- how biosimilars are monitored and tracked (pharmacovigilance)
- availability and access to biosimilar medicines.

Provide Information and Education

“There is a knowledge gap around the world and a need for government training and support. There needs to be a concerted effort from all and patients can advocate for this.” Fermin Ruiz de Erenchun, Biotherapeutics Group, International Federation of Pharmaceutical Manufacturers and Associations.

Particularly in the United States, where biosimilars are only just emerging into the market, unbiased education may not be available to patients and healthcare workers to learn about biosimilars and that these medicines are becoming available. Patients may not be presented with the information about what it means to be “highly similar” and the process involved to ensure products are safe and effective. Advocates can seek out opportunities to make healthcare providers aware of ways to best present this information to their patients and families so that it can be easily understood and readily available. Organizations and patient groups may benefit from assistance in developing educational messages about biosimilars that may be useful and understandable to their target audience and the general public.

Patients may not be aware that the treatment that is being recommended or prescribed may have a biosimilar alternative available. The first step would be to find out which biosimilars are currently approved by the US FDA, if they are available in your region and if so, when they may be added to the formulary of your healthcare facility. It may be of interest to find out if your facility or organization has a policy statement in place regarding biosimilars. Advocates can also approach their formulary inclusion review committee to find out the process by which new medications, and specifically biosimilars, may be considered for inclusion. It will also be important to understand any time delays that a review committee may have between the regulatory approval of a medicine and its approval for use in their facilities.

Join Biologic and Biosimilar Patient Groups

Patients for Biologics Safety & Access (PBSA) is a national coalition representing more than 20 patient advocacy organizations dedicated to protecting patient access to safe and effective biologics. The goal of the organization is to make sure the voices and interests of patients are heard as the FDA seeks to approve biosimilars. www.BiosimSafety.org

Provide Input

Throughout the FDA's development of guidance documents related to biosimilars, they have provided opportunities for public input. As an example, the FDA requested public input on, the benefits and challenges of other naming approaches, such as a suffix derived from the name of the license holder. They also seeking comment on the best approach to implement this naming convention for previously licensed products.

The FDA encourages the public to provide input on the FDA draft guidance and proposed rule by making comments to the appropriate dockets. They will consider all comments as they finalize the guidance and the rule. The FDA also invites the public to respond to the questions posed by FDA in the notice announcing the availability of the draft guidance and will consider these responses in finalizing the guidance and the rule. In order to receive notices or for more information, go to: www.fda.gov/biosimilars

For example, the PBSA has been a group actively providing input to proposed FDA guidance. "Patients for Biologics Safety and Access (PBSA) are pleased with the FDA's commitment to unique non-proprietary names of biosimilars. Unique distinguishable names for all biological medications are needed to ensure accurate tracking of medication utilization and adverse events, reduce patient and physician confusion and to enable a transparent system. PBSA will provide further suggestions to the FDA on issues on which they have requested more public input. One area we are particularly interested in is the development of and adverse event reporting system that is functional and universal."

The National Organization for Rare Diseases (NORD), a prominent patient advocacy group, has also provided input to the FDA, advocating for the adoption of "distinguishable names for biologics, including biosimilars."

Unified Pharmacovigilance and Adverse Event Tracking

As we have seen, a unified global approach to adverse event reporting and tracking system has not effectively been developed. As more biosimilar medicines become available globally, patients' organizations may wish to take the opportunity to advocate for improved pharmacovigilance systems worldwide. It may be useful to find out the process and guidelines used in your healthcare facility to report adverse events and the responsibilities of the physician, the pharmacist or other healthcare professionals.

Source

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Glossary of Terms

ACTIVE SUBSTANCE: Active ingredient or molecule which goes into a specific medicine and which provides this medicine with properties for treating or preventing one or several specific disease(s).

ADVERSE EFFECT: Any unintended or unfavourable event following the administration of a given medicine. An injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. Adverse effects may be preventable or non-preventable.

ANALYTICAL CHARACTERIZATION: Testing methods and techniques used to identify, isolate or quantify chemicals or materials, or to characterize their physical properties. They include microscopy, light or radiation scattering, spectroscopy, calorimetry, chromatography, gravimetric and other measurements used in chemistry and materials science.

ANTIBODY (PL: ANTIBODIES): Antibodies (also known as immunoglobulins, abbreviated to Ig) are large proteins that are found in blood or other body fluids. Antibodies are used by the immune system to identify and neutralise foreign objects, such as bacteria and viruses.

AUTOMATIC SUBSTITUTION: The practice whereby a pharmacist is obliged to dispense one medicine instead of another equivalent and interchangeable medicine due to national or local requirements without consulting with the prescriber.

BIOCHEMICAL CASCADE: (or a signaling pathway) A series of chemical reactions which are initiated by a stimulus (first messenger) acting on a receptor that is linked to the cell interior through second messengers (which amplifies the initial signal) and ultimately to effector molecules, resulting in a cell response to the initial stimulus. At each step of the signaling cascade, various controlling factors are involved to regulate cellular actions and responses.

BIOEQUIVALENCE: Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy.

BIOPHARMACEUTICALS/BIO TECHNOLOGY-DERIVED MEDICINES: A medicinal product or a vaccine that consists of or has been produced by the use of living organisms. Often recombinant DNA (a form of DNA that does not exist naturally and which combines DNA sequences that would not normally occur together in order to establish new functions) forms the basis for biotechnologically manufactured products. Examples include therapeutic proteins such as antibodies, insulins or interleukins; but also vaccines, nucleic acid or tissues and cells.

BIOLOGICAL MEDICINE (ALSO CALLED BIOPHARMACEUTICAL MEDICINE, BIOTECHNOLOGY MEDICINE OR BIOTHERAPEUTIC MEDICINAL PRODUCT): The active substance of a biological medicinal product is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source. A combination of physicochemical biological testing, the production process and control is needed to characterise it and determine its quality.

BIOSIMILAR MEDICINE: A biosimilar medicine is a highly similar version of an already-approved biological medicine, in terms of quality, safety and efficacy.

WHO definition of biosimilar (also called a similar biotherapeutic product): A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already-licensed reference biotherapeutic product.

EMA definition of biosimilar: A biological medicine that is developed to be similar to an existing biological medicine. When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.

FDA definition biosimilar: A biological product that is highly similar to a US-licensed reference biological product, notwithstanding minor differences between the biological product and the reference product in terms of safety, purity and potency of the product.

BIOTECHNOLOGY: The United Nations Convention on Biological Diversity defines biotechnology as "any technological application that uses biological systems, living organisms or derivatives thereof, to make or modify products or processes for specific use."

CHEMICAL AFFINITY: The electronic property by which different chemicals are capable of forming chemical compounds by binding together.

CHEMICAL MEDICINE/DRUG (ALSO CALLED SMALL MOLECULE MEDICINE): A medicine which is manufactured without the involvement of living organisms. These contain chemical compounds with defined structures and characteristics.

COMPARABILITY EXERCISE: Head-to-head comparison of a biotherapeutic product with a licensed originator product with the goal to establish safety, efficacy and quality. Products should be compared in the same study using the same procedures.

DNA (DEOXYRIBONUCLEIC ACID): DNA is a nucleic acid that contains the genetic information used in the development and functioning of all cellular organisms. DNA contains the genetic code that controls the production of proteins in all living things.

EFFICACY: The ability of a drug or medicine to produce the desired therapeutic effect when administered to a human.

EUROPEAN MEDICINES AGENCY (EMA): The EMA is responsible for approving all medicines before they are made available to doctors and patients in the 28 member states of the European Union.

ERYTHROPOIETIN: A hormone released from the kidneys and the liver in response to low oxygen concentrations in the blood. It controls the rate of red blood cell production.

EXTRAPOLATION: Using data from previously conducted studies in a particular patient population to justify the use of a drug in another group.

US FOOD AND DRUG ADMINISTRATION (FDA): The FDA is responsible for approving all medicines before they are made available to doctors and patients in the United States.

GENERIC MEDICINE: A generic medicine contains the same active pharmaceutical ingredient as and is bioequivalent to an original branded medicine. Since generic medicines are identical in the active pharmaceutical substance, dose, strength, route of administration, safety, efficacy and intended use, they can substituted for the original branded medicine.

GENOMICS: A discipline in genetics that applies recombinant DNA, DNA sequencing methods, and bioinformatics to sequence, assemble, and analyze the function and structure of genomes (the complete set of DNA within a single cell of an organism).

IMMUNE SYSTEM: The collection of mechanisms (or collection of biological substances and processes) within the body that protect against disease by identifying and killing pathogens (e.g. viruses and bacteria).

IMMUNE RESPONSE: A defence mechanism by the body in response to an invading substance, e.g. to bacteria, viruses and substances recognised as foreign and possibly harmful, through mechanisms such as antibody production, cell mediated response, or allergic or anaphylactic reaction.

IMMUNOGENICITY: The ability of a substance to trigger an immune response or reaction, e.g. the development of specific antibodies, cell-mediated response, or allergic or anaphylactic reaction.

IMPURITY: Any component present in the drug substance or drug product that is not the desired product, a product related substance, or inert substance including buffer components.

INSULIN: A hormone produced in the body that regulates the amount of glucose in the blood.

INTERCHANGEABILITY: The practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patients, or with the agreement of the prescriber.

INTERNATIONAL NON-PROPRIETARY NAME (INN): This name facilitates the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property, and is assigned by the World Health Organization.

MASTER CELL BANK (MCB): Homogeneous cell suspension derived from the original cell line. It is stored frozen in the vapour phase above liquid nitrogen in equal portions of uniform composition, one or more of which are used for the production of the manufacturer's working cell bank.

MECHANISM OF ACTION: (MOA) the specific biochemical interaction through which a drug substance produces its pharmacological effect. A mechanism of action usually includes mention of the specific molecular targets to which the drug binds, such as an enzyme or receptor.

MICROARRAY TECHNOLOGY: A collection of microscopic spots attached to a solid surface. Scientists use DNA microarrays to measure the expression levels of large numbers of genes simultaneously or to genotype multiple regions of a genome.

MOLECULE: The smallest particle of a substance that has all of the physical and chemical properties of that substance. Molecules are made up of one or more atoms held together by strong chemical bonds. If they contain more than one atom, the atoms can be the same (e.g. an oxygen molecule has two oxygen atoms) or different (e.g. a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins, can be made up of many thousands of atoms.

MONOCLONAL ANTIBODY (MAB OR MOAB): A class of antibody produced in the laboratory by a single clone of cells (parent cell or cell line) consisting of identical antibody molecules. Given almost any substance, it is possible to produce monoclonal antibodies that specifically bind to that substance; they can then serve to detect or purify that substance.

ORIGINATOR PRODUCT (ALSO CALLED INNOVATOR PRODUCT): A medicine which has been licensed by national regulatory authorities on the basis of a full registration dossier, i.e. that the approved indication(s) for use were granted on the basis of full quality, safety and efficacy data.

PATENT: A patent is a set of exclusive rights granted by a state (national government) to an inventor or their assignee for a limited period of time in exchange for public disclosure of its invention. Typically, however, a patent application must include one or more claims defining the invention which must be new, non-obvious, and useful or industrially applicable.

PHARMACOVIGILANCE: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

PHYSICOCHEMICAL: Pertaining to both physical and chemical properties.

PHYSIOCHEMICAL: Pertaining to both physiology and chemistry. Protein: Large organic compounds made of amino acids arranged in a chain. Proteins are essential parts of organisms and participate in virtually every process within cells.

PROTEOMICS: The identification and study of the proteins of a cell, tissue, or organism to determine their three-dimensional structure and to map their interactive networks to discover their function and the structure of drugs with the potential to interact in a therapeutic way with disease-associated proteins; goal is not only formulation of new drugs but also diagnostics and determining the presence of or absence of specific proteins associated with a disease or health.

RECOMBINANT DNA: DNA molecules formed by laboratory methods of genetic recombination (such as molecular cloning) to bring together genetic material from multiple sources, creating sequences that would not otherwise be found in the genome.

REFERENCE PRODUCT: A reference biotherapeutic product is used as the comparator for head-to-head comparability studies with the similar biotherapeutic product (biosimilar) in order to show similarity in terms of quality, safety and efficacy. Only an originator product which was licensed on the basis of a full registration dossier (full quality, pre-clinical and clinical data) can serve as a reference product.

REVERSE ENGINEERING: The act of taking something apart to understand its composition and how it works in order to duplicate or enhance the object.

RISK MANAGEMENT PLAN (RMP): The activities that will ensure that patients continue to be safe and experience benefit from a medicinal ingredient. These plans include pharmacovigilance plans among many other elements.

SUBSTITUTION: The practice of dispensing one medicine instead of another equivalent interchangeable at the pharmacy level without informing the prescriber.

SWITCHING: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.

TRANSGENE: A gene or genetic material that has been transferred naturally, or by any of a number of genetic engineering techniques from one organism to another.

Why Was this Guide Developed?

As advocates try to work within the system to advance research it is important to understand the basic tenets of the science. By gaining a better understanding, advocates can identify and illustrate the issues and problem-solve to support solutions. With the first biosimilar medicines being approved in the United State, it is important for advocates to understand the issues and possibilities these medicines represent for advancements in patient care. We hope that this information will be helpful to advocates and others interested in advancing the science and improving care for cancer patients.

About Research Advocacy Network

Research Advocacy Network is committed to improving patient care through research. Our goals are to get results of research studies for new treatments and improved methods of detection of cancer to patients more quickly, to give those touched by the disease an opportunity to give back and to help the medical community improve the design of its research to be more attractive to potential participants. Because research holds the hope for improvements in treatment, diagnostics and prevention, we are dedicated to patient focused research. We believe dissemination of research results to the medical community and patients can have a major impact on clinical practice.

The Research Advocacy Network (RAN) is a not for profit (501 c 3 tax exempt) organization that was formed in 2003 to bring together participants in the research process with the focus on educating, supporting, and connecting patient advocates with the medical research community. While there are many organizations addressing the needs of patients with specific diseases, political advocacy, cancer education and fundraising, no organization has focused on advancing research through advocacy. RAN works with advocates and organizations to effectively integrate advocates into research activities. Please learn more about us at our website at www.researchadvocacy.org or contact us about our work by e-mailing us at info@researchadvocacy.org or FAX at 888-466-8803.

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