Biosimilars Made Simple: A Micro-Analysis of Biosimilars & Relevant Policy

By: Lanton Law

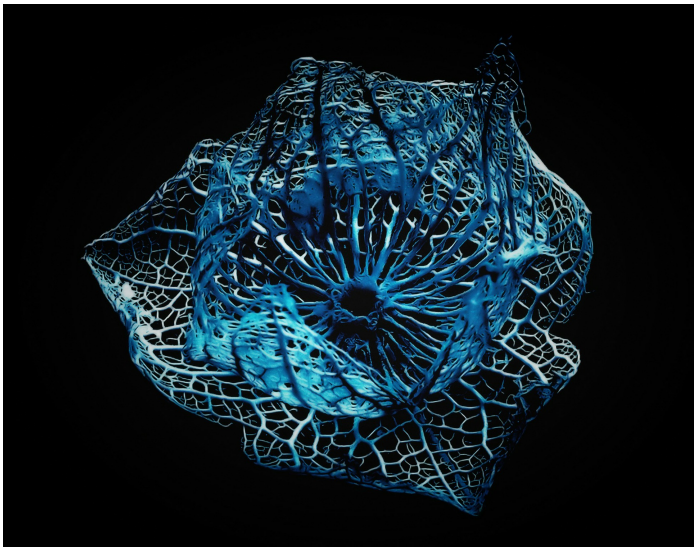
With the continued policy dialogue on how rising drug costs impact patient access, the theoretical cost savings that biosimilar medications may offer is intriguing to many stakeholders. A prior IQVIA found several interesting points regarding the potential of biosimilars:

- By 2020, biosimilars will start competing with original biologics that currently have sales of $50 billion annually.

- Biosimilar use in the European Union and the United States may yield total savings of $56 to $110 billion over the next five years.

- Healthcare systems, by opening markets to biosimilar competition, could realize a 30 percent reduction in price per treatment day compared with originator biologics.

There are many reasons that involve policy, legislation and the legal system that have led to the current state of the biosimilar market in the U.S.



With all this promise what is the disconnect regarding why we are not seeing increased market uptake? There are many reasons that involve policy, legislation and the legal system that have led to the current state of the biosimilar market in the U.S. Lets examine the basics to learn more.

What is a biosimilar?

A biosimilar is made from a living organism and is a highly-similar copy of the reference product (the biologic). There are no clinically meaningful differences in terms of safety and efficacy from the reference product that they are compared to.

Biologic vs. Biosimilar

Biological products are also made from living organisms. The material they are made from can come from many sources, including humans, animals, and microorganisms such as bacteria or yeast. Biological products are manufactured through biotechnology, derived from natural sources or, in some cases, produced synthetically. They are often referred to as the innovator or reference product in relation to the biosimilar.

Biological products are among the medications used to treat conditions such as rheumatoid arthritis, anemia, chronic kidney disease, autoimmune disorders, inflammatory bowel disease, skin conditions such as psoriasis and various forms of cancer.

Most biological products are more complex in structure and have larger molecules or mixtures of molecules than conventional drugs (also called small molecule drugs). Biologics themselves often have cold storage requirements and special handling instructions that most prescription brand drugs do not have. Biologics include a wide range of products such as vaccines, blood components, gene therapy, tissues, and proteins like cell signaling proteins.

The biosimilar is “similar” to the biologic but not an exact chemical copy. This is why the FDA has a different approval process for biosimilars than generics.

Biosimilars vs. Generics

- Approval

Generics : The Hatch-Waxman Act of 1984 made it possible for generics to be produced once a brand drug went off patent

- Approval is about how chemically identical the generic is to the brand.
- Generics save money via cheaper manufacturing and fewer trials.

Biosimilars: The Biologics Price Competition and Innovation Act of 2009 is the statute that created the abbreviated pathway for biosimilars.

- Biologics and biosimilars are made from living material.
- Approval is about how “similar” the biosimilar is to the brand biologic.
- Requires longer and larger clinical trials than a generic.
- Biosimilars only save money via less clinical trials than the biologic. They do not save money on the manufacturing process.

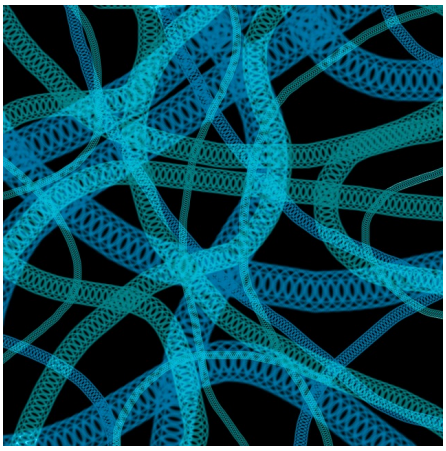
Price: Generics are significantly lower than their brand counterparts. Biosimilars are around only 30% less than the reference product. The process and added time biosimilars undergo in terms of proving similarities to the FDA, makes the biosimilar a lot more expensive than expected. There are many reasons why biosimilars are more expensive than a drug approved as a generic.

- The use of biologic material as opposed to chemical components
- Longer clinical trials.
- Higher costs spent on patent infringement cases
- Biologics may have longer exclusivity periods

Reimbursement: Generics are reimbursed under part D in Medicare. Payers prioritize generics as do many prescribers. Biosimilars are reimbursed under part B in Medicare.

- Medicare reimburses the average sales price (ASP) plus 6%.
- Prior to January 2018, ASP was calculated by grouping biosimilars that had the same HCPCS code or J code with the same reference product. All biosimilars had the same J code.
- Now each biosimilar has its own unique HCPCS code or J code and ASP information collected and calculated without the reference product information.
- Prior to ASPs becoming available, Medicare pays the Wholesale Acquisition Cost (WAC) plus 6% for the particular biosimilar product. WAC is a price set by the manufacturer.

How do ASPs become available? A manufacturer's ASP must be calculated by the manufacturer every calendar quarter and submitted to CMS within 30 days of the close of the quarter. Each report also must be certified by one of the following: the manufacturer's Chief Executive Officer (CEO); the manufacturer's Chief Financial Officer (CFO); or an individual who has delegated authority to sign for, and who reports directly to, the manufacturer's CEO or CFO.



Breakdown of FDA Biosimilar Approvals

First Biosimilar approved in 2015, Zarxio which Neupogen is the reference biologic.

Between 2015 and May of 2017 only four more would be approved.

Inflectra, Erelzi, Amjevita, and Renflexis

2017- 2018 saw an increase in approvals with 12 total. The uptick is likely due to the FDA Commissioner at the time; Scott Gottlieb who wanted to increase both generic and biosimilar utilization to lower costs.

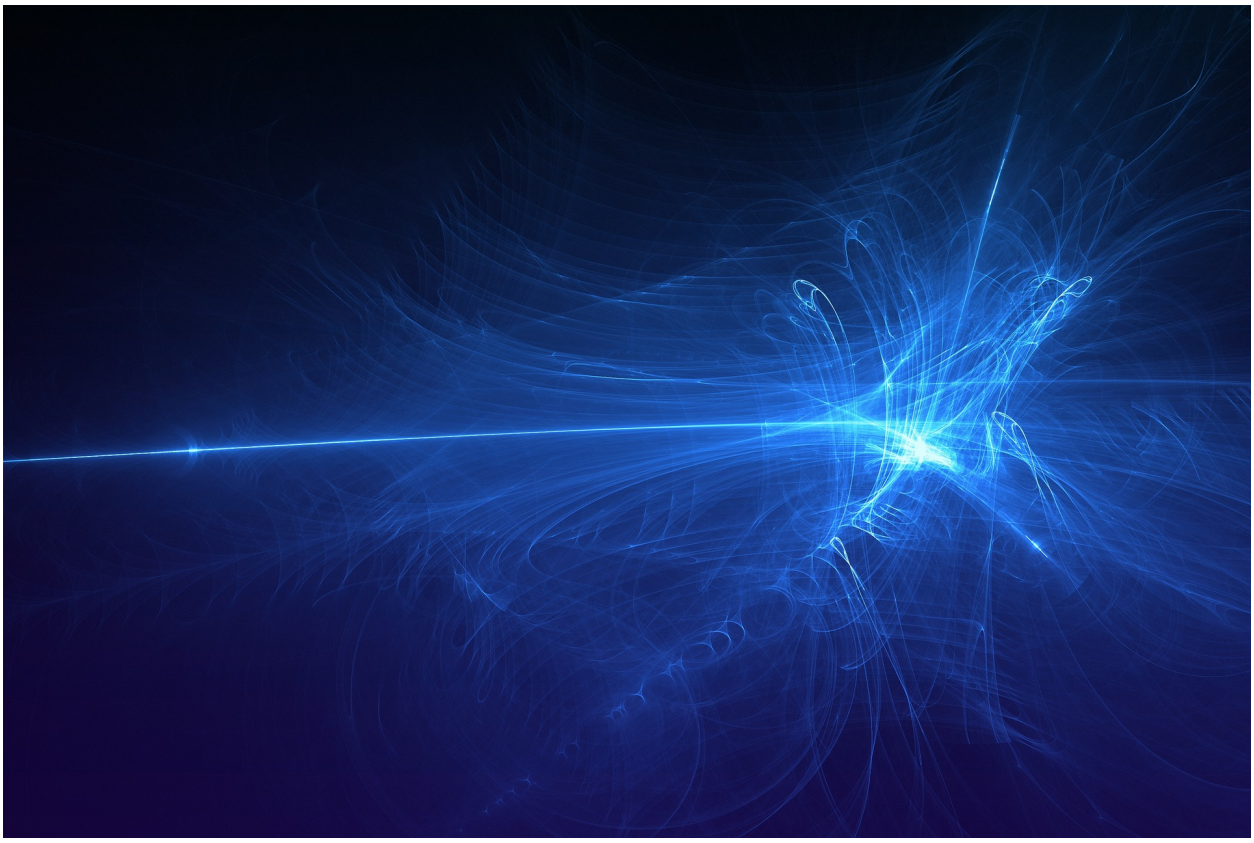
2019 saw 10 biosimilars approved. There are several biosimilars awaiting approval and in the pipeline. In total, the US has approved 26 biosimilars with only 12 total that have since launched.

Reference Biologic	FDA Approved Biosimilars
Enbrel (etanercept) **Treatment for RA and plaque psoriasis.**	Erelzi (etanercept-szzs) Eticovo (etanercept-ykro) Because of current patent protections these may not launch until after 2028.
Epogen / Procrit (epoetin alfa) Treats anemia.	Retacrit (epoetin alfa-epbx) Approved and launched in 2018 at a 33% discount to the reference product.
Herceptin (trastuzumab) Oncology treatment.	Ogivri (trastuzumab-dkst) Herzuma (trastuzumab-pkrb) Ontruzant (trastuzumab-dttb) Trazimera (trastuzumab-qyyp) Kanjinti (trastuzumab-anns) With a total of five biosimilars, Herceptin ties with Humira for the most biosimilars approved by the FDA. Out of those five biosimilars, two Ogivri and Kanjnti launched in 2019. With the launch of Trazimera in February that will make three competitors to Herceptin on the US market.

Humira (adalimumab) Treats Crohn's, UC and several types of arthritis including RA.	Amjevita (adalimumab-atto) Cyltezo (adalimumab-adbm) Hyrimoz (adalimumab-adaz) Hadlima (adalimumab-bwwd) Abrilada (adalimumab-afzb) There are five biosimilars too Humira that have to wait for commercialization until 2023. This is one of the most patent-protected innovator products.
Neulasta (pegfilgrastim) Reduces infection during cancer treatment.	Fulphila (pegfilgrastim-jmdb) Udenyca (pegfilgrastim-cbqv) Ziextenzo (pegfilgrastim-bmez) Coherus' Udenyca and Mylan/Biocon's Fulphila have captured 25% of the market in a little over a year. Ziextenzo launched last November at a 37% discount of Neulastas' WAC price.

Neupogen (filgrastim) Reduces infection for cancer treatment and bone marrow transplants.	Zarxio (filgrastim-sndz) Nivestym (filgrastim-aafi) Zarxio, by Sandoz, was the first biosimilar approved by the FDA in 2015 and launched the same year. The other biosimilar Nivestym was not launched in the US until October 2018.
Remicade (infliximab) Treats UC and Crohn's, RA and Plaque Psoriasis.	Inflectra (infliximab-dyyb) Renflexis (infliximab-abda) Ixifi (infliximab-qbtx) Avsola (infliximab-axxq) Inflectra launched in the US in 2016 with Renflexis following in 2017. Pzifer has decided not to launch Ixifi. Avosola has no launch date as it was the most recent biosimilar approved.
Rituxan (rituximab) For the treatment of adult patients with non-Hodgkin's lymphoma.	Truxima (rituximab-abbs) Ruxience (rituximab-pvvr) Ruixence recently launched in January of 2020 and Truxima launched in November of 2019.

Between the years of 2015 and 2017 only one biosimilar launched each year. This then tripled to a whole 3 in 2018. Last year, we saw a record 7 biosimilars launched in the US. Humira and Enbrel are the only two innovator biologics with FDA approved biosimilars that are not launched in the U.S.



Policy Basics (BPCIA and Transition)

The process of approval of biosimilars is governed by the Biologics Price Competition and Innovation Act of 2009 (BPCIA)

The BPCIA Act was enacted in 2010 with the intent of “balancing innovation and consumer interests” by creating an abbreviated pathway for the approval of biological products demonstrated to be biosimilar to, or interchangeable with, an FDA-licensed reference product.

To balance this abbreviated pathway for the development and approval of biosimilar and interchangeable products with incentives to develop innovative new products, the BPCI Act also provides exclusivity to manufacturers of certain biological products.

The FDA may not approve an application for a biosimilar or interchangeable product until 12 years after the date on which the reference product was first licensed. In the time since the enactment of the BPCI Act, the FDA has made substantial progress in developing the scientific and regulatory policies needed to implement this new approval pathway.

Specifically, drugs that will be transitioned are insulins and other naturally occurring proteins, such as hyaluronidase, human growth hormones, and menotropins.

The Transition

On March 23, 2020 the life sciences industry will undergo "the transition." Currently, the FDA has and will continue to regulate biologics but historically the FDA regulated biologics as drugs under the Food, Drug and Cosmetic Act instead of as products licensed under the Public Health Service (PHS) Act.

In order to bring all biologics under the same legal and regulatory system, the Biologics Price Competition and Innovation Act of 2009 (BPCIA) found in the ACA included the "Deemed to be a License" provision. This meant that 10 years after enactment (3/23/20) applicable biologics will automatically be deemed biologics licensed under the PHS Act. Unfortunately, the statute did not provide instructions to the FDA on how to do this, meaning the FDA will decide on which products transition and how.

This basically means no more new drug applications or abbreviated new drug applications for select biologics, only biologic license applications of the 351(a) and 351(k) varieties. Also not only will they be categorized as biologic but they will be subject to the biosimilar, not generic competition.

Specifically, drugs that will be transitioned are insulins and other naturally occurring proteins, such as hyaluronidase, human growth hormones, and menotropins.

So it will be harder to measure "true uptick" in biosimilars as these transition drugs have not been part of the biosimilar market as we have known it.

If I could suggest one area of policy to follow in biosimilars is to follow the transition closely. The FDA has already started the process with insulin products and this will have an impact on interchangeability and utilization.

Policy Basics (Interchangeability)

There are two pathways for approval of a biosimilar in the US. The first is being approved simply as a biosimilar. A biosimilar will only gain FDA approval if it has the same mechanism of action, route of administration, dosage form, and strength as the reference product itself. Furthermore, it can only be approved for indications previously approved for the reference product. It can also go through an additional pathway to be approved as interchangeable. This requires more data from the drugmaker and a separate application fee. There are no biosimilars on the US market that carry interchangeable designations.

Interchangeability is the practice of exchanging one medicine for another medicine with the exchanged medicine having the same clinical effect. Basically, replacing a reference product with a biosimilar in treatment and vice versa.

This can happen in two ways:

Switching: When the prescriber decides to exchange one medicine for another medicine for the same treatment or therapeutic effect. Once a biosimilar has an interchangeable designation a prescriber can switch the biosimilar for the biologic instead of prescribing the biosimilar as the original treatment.

Substitution: This is the automatic practice of dispensing one medicine instead of another medicine at the pharmacy level without consulting the prescriber. This is done now with generics. The states are in charge of most prescriber dispensing practices.

A majority of states have passed laws that allow for the substitution of biosimilars once there is interchangeability. 47 states have passed some form of biosimilar substitution legislation Currently there are no biosimilars that are interchangeable with their reference product. This is another way that biosimilars are different from generics. The process for substitution is in two steps. First, the biosimilar is approved then it must go through a second approval process for interchangeability.

The laws all have some sort of reporting back to the prescriber and minimum record-keeping requirements. States are getting ready and have passed legislation allowing for substitution. Almost every state has a way for a pharmacist to substitute a biosimilar for its reference product.

It is also important to know how to give notice of substitution to a physician. Many states have an interoperable electronic system that the parties must communicate by but has not been built. Developing this can be expensive and determining what interoperable is can be problematic as seen with the policy development around drug pedigree.

Europe vs The U.S.

A quick history of biosimilars in Europe:

The EU was the first to define a legal framework for the approval of biosimilars. The first legislation was introduced in 2001 and after several adjustments, a complete directive (this is the legal act in the EU) was in place by 2004. It gave the European Medicines Agency the responsibility of evaluating applications for biosimilars in the European Union.

Europe passed regulatory procedures for biosimilars in 2005. With a legal framework in place, the EMA then worked on a complete regulatory process and released guidelines to deal with all aspects of the development, production, testing, and regulation of biosimilar medicines. By 2006 specific guidelines on quality, clinical, and nonclinical issues relating to the development of biosimilars were added. The EMA continues to update the regulatory framework.

According to the EMA it “evaluates biosimilars by the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines approved in the EU.”

“Developers of biosimilars are required to demonstrate through comprehensive comparability studies with the 'reference' biological medicine that:

- their biological medicine is highly similar to the reference medicine, notwithstanding natural variability inherent to all biological medicines;

- there are no clinically meaningful differences between the biosimilar and the reference medicine in terms of safety, quality and efficacy.”

The first biosimilar approved in 2006, was Omnitrope by Sandoz. The drug is indicated for the treatment of growth disorders in children and adults.

It took Europe only one year to approve its first biologic whereas the U.S. took over 5 years.

Biosimilars have been used for almost twice as long. Europe pioneered the process for approval and in doing so has a large lead in data and innovation over the United States. The lag time of almost ten years for the United States to even approve a biosimilar is the main difference between the U.S. and Europe.

Essentially the scientific innovation was there the entire time but US has a different system than the EU, it took longer for policymakers to realize the need for a specific pathway for biosimilars and therefore a specific market.

Policy differences

But why? This suggests that the US was not a scientific innovator in this area. We at Lanton Law suggest that this is not the case.

Omnitrope was also approved for use in the United States in 2006 using the 505(b)(2) pathway of the Hatch-Waxman Act, becoming the first recombinant copy of a biotech drug to be **approved** in this manner. Basically, the US still approved a biosimilar just as a "bio-generic" with the differences between generics and biosimilars not becoming apparent to policymakers until they created the Biologics Price Competition and Innovation Act of 2009. Until then there was no specific biosimilar market in the US.

Ultimately, there was no way to measure a market until the US actually created a "biosimilar" designation for its products. Hence, Europe's innovation in policy-making created its biosimilar market faster than the US. Once the US finally created the market, the FDA then had to create its own regulatory framework that would work. We could even say that the FDA's regulatory drafting process was slower than Europe's and this added more to the lag time. Essentially the scientific innovation was there the entire time but because the US has a different system than the EU, it took longer for policymakers to realize the need for a specific pathway for biosimilars and therefore a specific market.

The regulatory process between the US and Europe is generally the same for a few differences.

- Interchangeability is not addressed in Europe as they leave substitution up to member countries. As mentioned earlier, interchangeability is an additional designation given by the FDA in order to allow substitution of a biosimilar for a biologic. This is a major difference with Europe because the EMA does not interfere in member state's decisions allowing for innovation across the EU in the utilization. It takes away the backdrop of generic policy and gives member states space to make decisions regarding interchangeability with or without a specific designation.

- "When the EMA carries out the scientific review of a biosimilar the evaluations do not include a recommendation on whether a biosimilar is interchangeable with the reference product and thus whether the reference medicine can be switched or substituted with the biosimilar." *EMA statement of policy October 2019.*

- Europe has approved over 50 biosimilars to date. It varies by individual country, but we see about 30-40 biosimilars on the market in any given EU country. That is still much higher than in the US.

Patent Dance

The law (BPCIA) that created the biosimilar pathway in 2009 also created a patent dance. Policymakers set out requirements for the exchange of information between the reference product patent holder and the biosimilar license applicant. In doing so they hoped to resolve potential patent disputes effectively. This is called the patent dance. Here is how it plays out.

Round One

1. Within 20 days of the FDA's acceptance of the biosimilar application: a biosimilar applicant provides the reference product sponsor confidential access to its full application. The biosimilar applicant can also provide the reference product sponsor detailed information concerning the biosimilar product's manufacturing process

2. 60 days after the first exchange: the reference product sponsor must provide the biosimilar applicant with a list of unexpired patents for which a claim of infringement could reasonably be made, as well as any licensing offers.

3. After receiving the patent list, the biosimilar applicant has 60 days to provide detailed invalidity, unenforceability, and/or non-infringement contentions for each of the asserted patents. It basically gets to prove its case that it is not violating patent law.

Round Two

"Notice of commercial marketing" within 180 days by the biosimilar maker. This is the biosimilar telling the innovator that they plan to launch the product. Both parties can then start new litigation after this notice. This can include, innovators bringing actions for injunctive relief based on non-asserted (but previously listed) patents, and applicants can bring declaratory judgment actions for invalidity, unenforceability, and/or non-infringement against any innovator patent not pursued during the first phase.

This is the patent dance that needs to be strategized by each applicant ahead of time or it may slow down the launch of a product. The first biosimilar approved by the FDA Zarxio by Sandoz tested this very dance and it resulted in the first Supreme Court interpretation of the BPCIA.

Amgen vs. Sandoz

Amgen vs. Sandoz is the major Supreme Court case that answered specific questions about when and how a biosimilar could be taken to market.

Issues include when the 180-day notice of launch is required and what information needs to be shared. The first major interpretation of The Biologics Price Competition and Innovation Act came down mostly in favor of biosimilars.

Sandoz applied to the FDA for approval of Zarxio in 2014. They refused to enter the patent dance by not giving Amgen its full application and manufacturing process. Amgen brought suit in federal district court asserting the BPCIA patent dance was mandatory. After two appeals by Amgen, the Supreme Court took up the case.

There are two issues that were answered by the Court in this case, which revolved around Sandoz's biosimilar Zarxio an approved biosimilar of Amgen's Neupogen.

- Did Sandoz; makers of the biosimilar product in question, give proper notice to Amgen of its intent to market a biosimilar of Neupogen?
- Is Amgen entitled to an injunction; stopping Sandoz's application to the FDA until Sandoz gives Amgen its research and FDA application?

Sandoz and its biosimilar clearly won out on the first question. The court stated that the biosimilar manufacturer could simultaneously enter its application to the FDA and give notice of its intent to market to Amgen. This part is the most important part as it allows the biosimilar to reach the market faster.

Amgen wanted the court to rule that the FDA application had to be approved before the notice of intent would be allowed. In ruling for the biosimilar, the Court denied Amgen more time to exclusively market Neupogen without biosimilar competition.

On the second question of the injunction, the Court ruled that the question did not need an answer. Amgen had received the application and research information from Sandoz in discovery.

Here, the Court intended to be cautious as they were not sure if the BPCIA barred the makers of brand-name biologics from obtaining relief in state court. And, it did not rule on whether the states could issue an injunction and remanded to the federal circuit court. Since then Amgen has lost again as the federal circuit court ruled against them stating that their state relief claims

were preempted by the BPCIA. All the while Zarxio was approved by the FDA and launched by Sandoz in 2015.

This decision has consequences for the makers of brand biologics, who are trying to protect their patents. With the required notice of intent to market being 180 days, it's possible that, if the FDA takes 180 days to approve a biosimilar application, the biosimilar can immediately start to market its treatment.

Sandoz took a huge chance in not engaging in the patent dance. It paid off for Sandoz and other biosimilars. During this time, which was 2014 to 2017 many other biosimilars makers were having to take these chances without any legal assurances. This may be one of the many reasons why the market was slow during these years. Now with this issue answered innovators such as Amgen are using the same patent thicket that this very patent dance was trying to alleviate.

Patent Cliffs and Patent Thickets

Patent Cliff: What is the patent cliff? When a patent expires and there is a fast drop in sales after the expiration. This happens with a group of products that are a high percentage of the market. This happened recently with a group of biologics. Several went off patent a few years back and this is why we saw so many biosimilars gain approval over the past few years. It's also why you have seen the earnings of some well-known names drop.

Patents set to go off the cliff: Humira will face competition in 2023 and most of its patents will continue to expire. Remicade patents have already expired and Stelara will face expiration in 2022. Celgene's Revlimid will face limited competition in 2022 and key patents for Novo Nordisk's Levemir expired in 2019 in the US and Europe. These are major expirations in the anti

inflammatory, chemotherapy and diabetes markets. I am including all of these drugs here as the transition will make all of these drugs possibly subject to biosimilar competition, especially insulin.

Patent thicket: A dense forest of overlapping patents of an innovator's product that must be slowly hacked through in order for the commercialization of the biosimilar.

Example: Humira has been one of the biggest selling drugs in the world. Its main ingredient patent expired in 2016. There are 136 patents held by its maker AbbVie that creates a patent thicket that will last until 2023. That is 20 years after the drug was first introduced. What are they doing to avoid the patent thicket?

- Biosimilar makers are starting to stay out of the patent dance and negotiate with the brand in order to come into the market. This is what Amgen did with Abbvie in order to start selling its biosimilar of Humira in 2023.
- Buying or creating its own generics/biosimilars, Amgen has several patents for both brand biologics and biosimilars.
- Focusing on other disease states. Gilead moved its main focus from Hep C to HIV in an effort to stem its losses.

The future of biosimilars is for greater approval numbers and utilization. The issue is what the transition will do to the current market as new types of biosimilars such as insulins get approved.