BIOSPECTRA
Premium Pharmaceutical Ingredients

An Overview of the BioPharmaceutical Products and Market

By Paul DiMarco, Vice President, Global Commercial Program, BioSpectra Inc.

Table of Contents

INTRODUCTION:

1. A Biosimilar is to a biological as a Generic is to an original synthetic drug.[1]
2. A Biosimilar is a biotherapeutic intended to compete with an already marketed biological drug.[2]
3. **The original biological drug is called the *reference product* or *reference drug*. The company that manufactured the original biological entity is called the *innovator*.[3]**
4. The expectation for approval by the FDA is that a Biosimilar will arrive on the market at 20-30% lower in cost than the reference biological.[4] Therefore, stakeholder agencies have created abbreviated approval pathways to keep costs of development and approval *manageable* and these goals achievable.[5]
5. Most synthetic drugs are sufficiently small enough (i.e. small molecules) that an identical *generic* version can be synthesized.[6]
6. Unlike traditional synthetic (small molecule) drugs, most Biological drugs are massive in comparison. The molecular weight of a small molecule **drug** is typically less than 1 kDa (20–100 atoms), whereas the molecular weights of **biologics** range from a few kDa to 1000 kDa (ie, IgM mAbs). The efficacy and safety of therapeutic proteins are also affected by their secondary, tertiary, and quaternary structures.[7] Therefore the "generic" version cannot be identical but only "similar" and hence, the generic version of a biological drug is called a "Biosimilar".
7. Even two batches of the same biological drug are "similar" and not identical. Because of this the way that biologicals are characterized is different than traditional synthetic small molecule drugs. Batch to batch a biologic reference product exhibits clinically non-meaningful differences given the variability of biologic molecules.
8. This creates a whole set of challenges and opportunities both for the drug developer and companies who would like to sell raw materials into this market.

History

1. **Vaccines and insulin fall into an older, different category as biological products.**
2. A vaccine is a biological preparation containing an "agent" that is used to stimulate the production of antibodies.[8]

---

[1] "What Are Biosimilars?," Biosimilars Resource Center, accessed August 11, 2020, https://www.biosimilarsresourcecenter.org/faq/what-are-biosimilars/.

[2] "FDA," FDA § (2018), https://www.fda.gov/drugs/generic-drugs/generic-drug-facts.

[3] "Biologics & Biosimilars," PhRMA Org, accessed August 11, 2020, https://www.phrma.org/Advocacy/Research-Development/Biologics-Biosimilars [emphasis added].

[4] See note 3 above.

[5] "FDA," FDA § (2018). [emphasis added]

[6] "FDA," FDA § (2018). [emphasis added]

[7] Liang Zhao, Tian-Hua Ren, and Diane D Wang, "Clinical Pharmacology Considerations in Biologics Development," Acta Pharmacologica Sinica 33, no. 11 (2012): pp. 1339-1347, https://doi.org/10.1038/aps.2012.51.

[8] "Vaccine," in Merriam-Webster, accessed August 11, 2020, https://www.merriam-webster.com/dictionary/vaccine.

3. Vaccines started in 1926 (Diphtheria), followed by Pertussis in 1948 and then measles, mumps and rubella in 1963, 67 and 69 respectively. These were combined into the MMR vaccine in 1971.
4. **Insulin is a reasonably small protein hormone produced in the pancreas that regulates the amount[9] of glucose in the blood with 51 amino acids and a molecular mass of 5808 Daltons (Da).**
5. Synthetic insulin is made from both bacteria and yeast. In this sense the word "synthetic" does not mean synthetic organic chemistry but rather made by a biological process controlled by man.
6. **Synthetic Insulin was the first golden molecule of the biotech industry and the direct result of** recombinant DNA technology (i.e. use of genetically modified organisms). First developed in 1978, the first commercially available biosynthetic human insulin was produced and sold by Eli Lilly (now just Lilly) in 1982 under the brand name Humulin.[10]
7. **In the eighties and nineties many biological drugs were created and launched. These are now coming off the 20-year patent cycle for Biologicals, and as such the next 10 years will experience a massive increase in biosimilars being developed and attempting to enter the market.**
8. The first Biosimilar approved in the EU was in 2006 and in the US in 2015.
9. **Biologicals on the market are all block buster drugs (multi-billion per year). For every Biological there could be multiple companies developing Biosimilars.**

Background information

1. **In 1984 the US Drug Price Competition and Patent Term Restoration Act** (otherwise known as the Hatch-Waxman Act) ushered in the revolutionary small molecule generics industry. **This allowed pharmaceutical companies to create identical, more cost-effective copies of small molecule brand name drugs that were facing patent expiration. The goal was lower cost and hence accessibility to the US public.[11]**
2. **Today 90% of all drugs dispensed in the US are generic drugs which account for only 26% of total drug costs.[12] Small molecule generic drugs have been estimated to save the US healthcare system roughly $1.7 trillion USD.[13]**
3. Due to the high costs of innovative drug development (estimated at somewhere between $1-3 Billion USD for small to large "blockbuster" drugs) the US government (and others in suit) provide

[9] "What Are Biosimilars?."

[10] "Insulin," Wikipedia (Wikimedia Foundation), accessed August 11, 2020, https://en.wikipedia.org/wiki/Insulin.

[11] "FDA," FDA § (2018), https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/hatch-waxman-letters.

[12] Rachel Schwartz, "Association for Accessible Medicines ," Association for Accessible Medicines (blog), accessed August 7, 2020, https://accessiblemeds.org/resources/blog/generic-drug-supply-chain.

[13] Hiten J. Gutka, Harry Yang, and Shefali Kakar, eds., Biosimilars: Regulatory, Clinical, and Biopharmaceutical Development, vol. 34 (Cham: Springer International Publishing, 2018), https://doi.org/https://doi.org/10.1007/978/-3-319-99680-6, 4.

defacto patent protection through **market exclusivity** for a **period of 20 years**. Though, by the time a company fully develops and clears the clinical trial process it turns into **10-12 years on average**.[14]

4. **Despite the enormous costs of development and cost of the drug, sales are expected to reach $500B for Biologicals and 10% of that for Biosimilars $44.5 Billion USD in 2026.[15]-[16] It is further expected that by 2020, 50% of all spending for the top 100 drug sales will be on Biologics and Biosimilars even though that will account for only 20 of those top drugs.**
5. **The driving concept behind Biosimilars is that it will decrease the cost of healthcare in the same way small molecule generic drugs have.**
6. **Global spending on medicine is forecasted to reach $1.6 trillion (USD) by 2024.[17] With the populations of China and India increasingly becoming more consumer and health orientated medical costs will continue to climb at dramatic rates.**
7. Majority of this growth being incurred by oncology, autoimmune and diabetic medicines.

Defining biological products

1. **A small molecule drug contains an active ingredient that typically weights less than 1000 Daltons** (Da). A large molecule dwarfs this by comparison. For instance, Aspirin is 180 Da (MW = 180 and 1[18] mole of aspirin would weigh 180 grams (1.8 kg), whereas a **monoclonal antibody can be 150,000 Da** and be comprised of **20,000 atoms.[19]**
2. **Product derived from human, animal, or microorganism sources: Protein-based hormones, enzymes, monoclonal antibodies, vaccines, blood products and gene and cellular therapies.** The first of these products were approved in the 1980's, most of which being produced by GMOs. Example: Monoclonal antibodies were made by clones of a genetically modified parent cell.
3. **A Biosimilar has three basic tenants[20]:**
    a. It must be a biologic.
    b. It must contain a version of the active substance found in the reference product.

[14] "Drug Approvals - From Invention to Market...12 Years!," MedicineNet, accessed August 11, 2020, https://www.medicinenet.com/script/main/art.asp?articlekey=9877.

[15] John Watson, "Biosimilars Market To Reach USD 44.56 Billion By Year 2026: Reports And Data," Intrado ("GlobeNewswire", March 19, 2019), https://www.globenewswire.com/news-release/2019/03/19/1757249/0/en/Biosimilars-Market-To-Reach-USD-44-56-Billion-By-Year-2026-Reports-And-Data.html.

[16] Avik Roy, "Biologic Medicines: The Biggest Driver Of Rising Drug Prices," Forbes (Forbes Magazine, March 8, 2019), https://www.forbes.com/sites/theapothecary/2019/03/08/biologic-medicines-the-biggest-driver-of-rising-drug-prices/.

[17] Matej Mikulic, "Global Spending on Medicines 2024 Forecast," Statista, May 25, 2020, https://www.statista.com/statistics/280572/medicine-spending-worldwide/.

[18] "Biologics & Biosimilars," PhRMA Org, accessed August 11, 2020, https://www.phrma.org/Advocacy/Research-Development/Biologics-Biosimilars.

[19] Zhao, Ren, Wang. "Clinical Pharmacology."

[20] Gutka, Yang, Kakar, eds., 4

   c. It must embody highly similar quality characteristics, biological activity, safety and efficacy profiles to those of its reference product.[21]

4. **The development pathway and approval (in the US the 351(k) pathway) is based on analytical similarity and is a step by step process of research and adjusting manufacturing processes to achieve acceptability (by the FDA or EMA) to move forward with the appropriate clinical studies to eliminate any residual uncertainty.[22]**
5. Biosimilar development pathways vary but generally follow the World Health Organizations guidelines.[23]
6. Biosimilar are also referred to as—
   a. "subsequent entry Biologics"
   b. "biogenerics"
   c. "similar biological medicinal products"
   d. "follow-on proteins"
   e. "follow-on biologics"
   f. "similar biotherapeutic products"
7. **Advancements in manufacturing and other areas of science have allowed for the next generation of Biologics – much larger and more advanced therapies.**
8. **Unlike small molecule pharmaceutical/generic drugs that employ organic chemical synthesis as the primary route to create the active substance, large molecule biologic/biosimilars have highly complex manufacturing processes utilizing living cells (bacteria, yeast and mammalian), administration methods that require infusion or injection and complex immunogenic profiles. These cells are genetically modified to express a specific protein which will selectively bind to a specific disease target (e.g. cancer cell receptor).[24]**
9. A small molecule can be formulated into tablets or capsules and taken orally and easily absorbed into the bloodstream. There is also little to no chance that a small molecule will invoke immunogenicity (an immune response that could lead to severe adverse events for the patient or render the drug ineffective over time.)
10. **In difference, biologics are highly variable and as such, are sensitive to manufacturing changes, heat and cold. Hence the importance of refrigeration and a well-developed cold chain for biologics. They cannot be taken orally as the primary structure of a protein is a peptide bond and highly susceptible to acidity.**
11. **Biologics hold the potential to be immunogenic.** Large enough differences in the molecular structure could potentially alter the drug's safety and efficacy over time.
12. Due to these fundamental differences there is a massive difference in cost and timeline for commercialization of a generic vs. a biosimilar drug:
    a. **$1-5M in cost over 3-5 years for a generic drug**

[21] Gutka, Yang, Kakar, eds., 4
[22] Gutka, Yang, Kakar, eds., 4
[23] Gutka, Yang, Kakar, eds., 4
[24] Gutka, Yang, Kakar, eds., 4

   b. **$100M to $200M over 8-10 years for a biosimilar[25]**
13. **Regardless of these challenges the enormous potential for billions in revenue has caused a "biologicals tidal wave" that has swept through the pharmaceutical and healthcare space.**

Small vs. Large Molecule Regulation and Registration in the USA and EU

1. Like generics, the regulatory pathway to approval (EMA, FDA) is abbreviated to decrease the costs of development and encourage a quicker path to market. This too is a subject of great controversy, particularly with the FDA.
2. **One of the largest advantages granted in the abbreviated approval process is allowing the Biosimilar to be approved for almost every indication (therapeutic application) of the original biological reference drug without having to perform separate clinical studies for all indications (orphan indications excluded).**
3. NDA: New drug application for a novel small molecule.
4. ANDA: filed for the generic version.
5. **The drug maker filing the ANDA does not need to independently gather evidence of safety and effectiveness. It only must prove it contains these following items compared to the reference product it is copying:[26]**
   a. the same active ingredient(s)
   b. conditions of use
   c. route of administration
   d. dosage form
   e. dosage strength
   f. labeling
6. **The ANDA must also demonstrate the generic drug is bioequivalent to its reference product using in vivo (in human) or in vitro (non-human) testing, or both depending on the product.**
7. **A company seeking approval for a novel biologic in the US must file for a Biologics License Application (BLA) which comprises manufacturing information, preclinical and clinical study data as well as labeling information. Like a novel small molecule drug, most of the safety and efficacy data is gleaned from a large complement of human clinical trials.**
8. A biosimilar is also approved using a BLA however it follows the FDA's 351(k) pathway. This pathway dictates that a biosimilar maker does not need to recreate all the same steps as the reference product. **Rather a biosimilar maker must:**
   a. **Submit analytical studies showing molecular similarity to the reference product**
   b. **Animal studies, including toxicity assessment**

[25] Erwin A Blackstone and P. Fuhr Joseph, "The Economics of Biosimilars," Am Health Drug Benefits 6, no. 8 (2013): pp. 469-478, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/.

[26] "FDA," FDA § (2019), https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda#:~:text=An%20abbreviated%20new%20drug%20application,of%20a%20generic%20drug%20product.&text=To%20be%20approved%20by%20FDA,time%20as%20the%20innovator%20drug.

   c. **One or more studies in at least one indication (application) to demonstrate safety, purity and potency.**
   d. **One study must at least be an immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD) study.**
   e. **Common regulatory protocol requires a sponsor to investigate the candidate in a phase 1 PK/PD study with healthy volunteers and a phase 3 clinical study comparing safety, efficacy and immunogenicity to that of the reference product in one of the applied-for indications.**

9. Whether NDA or ANDA for a biologic/biosimilar the company needs to amass four types of data:
   a. Analytical
   b. Nonclinical
   c. Clinical pharmacology
   d. Clinical studies
10. **Biosimilar approvals rely on the "totality of the evidence". For a novel biologic, the largest amount of data comes from the clinical studies section, but for a biosimilar it's the analytical section.[27]**
11. **The most important takeaway for biosimilar development and the regulatory process is that a biosimilar does not need to independently re-establish safety and efficacy.**
12. **The EU is 10 years ahead of the US in approving biosimilars with somatropin, erythropoietin and filgrastim being approved by the EU in 2006, 2007 and 2008 respectively. As of July of 2017, the EU had approved 30 biosimilars with 26 launches.[28]**
13. **In contrast, it wasn't until 2015 that the US saw the approval of its first biosimilar, Sandoz's Zarxio, a biosimilar of Amgen's Neupogen (filgrastim). As of August 2017, only three more had been approved. This has led to severe criticism of the FDA and scrutiny of the approval process.**
14. Why? In addition to the FDA seemingly (always) being more difficult to work with than the EMA, the EU's healthcare costs burden individual country governments to a much greater degree than in the US where the impact is more so on the private sector and individual citizens. This has led to increased acceleration of the approval process and acceptance in the EU versus the USA.

Controversial Regulatory Concepts:

Biosimilars have created a paradigm shift in terms of how they are developed and assessed by regulators creating several key regulatory debates:

Extrapolation[29,30]:

   a. Extrapolation is based on the concept that the structure of the protein is responsible for its therapeutic efficacy.

[27] Gutka, Yang, Kakar, eds., 4
[28] Gutka, Yang, Kakar, eds., 4
[29] "Vaccine," in Merriam-Webster, accessed August 11, 2020, https://www.merriam-webster.com/dictionary/vaccine.
[30] Gutka, Yang, Kakar, eds., 9 to 15.

b. **This is when the successful approval of a biosimilar for one indication (therapeutic application) automatically provides approval for all other indications (excluding orphan indications) even though comparative clinical trials have not been performed in each condition.** Thus the 351(k) process provides an enormous advantage to the company making the application.
c. While highly controversial, it is hardly novel in the biologics world where extrapolation has become routine for all biologics following major changes in their manufacturing process.
d. Even reference products exhibit clinically non-meaningful difference from batch to batch given the variability of biologic molecules and the need to alter manufacturing processes.
e. Following these process changes, its customary for the biologics company to perform analytical and non-clinical characterization and comparability to the reference molecule to ensure it still lies within the approval limits and not alter clinical performance. The biologic in these cases is not required to re-demonstrate safety and efficacy in clinical trials.
f. Differences between a biosimilar and the biological reference molecule are less than the changes in the biological reference molecule following process changes in the biologic's life cycle.
g. Thus, reliance on analytical methods to demonstrate similarity following manufacturing changes essentially justifies biosimilar extrapolation.
h. Analytical characterization has at its root the exhaustive study and comparison of the primary, secondary and tertiary structure of the protein and the mechanism of action. These are chemical, physical and biological comparisons.
i. The rule to allow extrapolation eliminates the need for exhaustive and comprehensive clinical trials for all indications thus greatly lowering the cost of development.
j. Despite these commonly accepted concepts by scientists, acceptance is not always easily transferable to the target community of doctors and patients. It has been exceptionally challenging for physicians and patients to grasp the concept of approving a "highly similar but not identical" biologic for multiple conditions without seeing clinical data in all the indications.

Switching:[31]

k. Switching from a biologic to a biosimilar or from one brand of biosimilar to another (multiple switching).
l. Its one thing to have the doctor prescribe the biosimilar to a new patient and quite another to "switch" the patient from the original biologic to a biosimilar. This is an area of controversy regarding cost and insurance companies (switching can occur at the pharmacy level. Doctors in the US are forced to demand non-switching and patients may have to fight with insurance companies as well).
m. Multiple switching also has raised many concerns due to the lack of clinical studies.

[31] Gutka, Yang, Kakar, eds., 9 to 15.

Interchangeability:[32]

n. A declaration by the FDA that the biosimilar is in fact completely interchangeable with the reference biologic expected to produce the same clinical result as the reference product in any given patent.
o. Without the declaration the FDA has put the burden (or the power) on the physician to determine if the switch is safe.
p. Once declared "interchangeable", however, the drug can be switched at the pharmacy level without the intervention of the physician who prescribed it.
q. This can only occur with further testing and clinical trials. A big break from the EU practice (which does not take a stand on interchangeability) and a departure from small molecule generic drug practice, acceptance and switching practices in the USA.

Harmonization:[33]

r. World Health Agencies are not harmonized on these and other concepts regarding biosimilars, in particular, the FDA, EMA, Health Canada, and PMDA (Japan).
s. The FDA and EMA are working more closely together where others slowly adopt these changes.
t. Lack of harmonization requires drugs to be launched separately in these large economic blocks increasing costs for the industry overall.

Patent Battles as a form of market protection and extending a defacto-period of exclusivity: [34]

Market production: Outside of the original 20-year market exclusivity granted by the FDA Big Pharma attempts to extend its market control through patent battles.

1. **A single biological can have 20-30 patents** for its manufacture, formulation, delivery and packaging as well as for its application.
2. **It is common for the biological company to sue** anyone and everyone attempting to infringe on patents, often obtaining injunctions that extend the defacto exclusivity for many years.
3. Biosimilar companies have fought back with counter suits
4. **As Big Pharma gets involved** in both sides of the game, mega-suits have increased with mega-settlements and all kinds of compromises.
5. **Exclusivity is justified** when you look at the "odds" the innovator faces: Only 5 out of 1000 initially investigated become approved drugs for clinical trial, and only 5-10% of those drugs that successfully clear the clinical trial process to become approved by the FDA. Daunting numbers! On top of that only 30% of all drugs become profitable over the drugs life cycle. That is a 0.025-0.05% success rate for commercialization and even less for profitability (.0075-0.015%), barely 1/100th of 1

[32] Gutka, Yang, Kakar, eds., 9 to 15.
[33] Gutka, Yang, Kakar, eds., 9 to 15.
[34] Gutka, Yang, Kakar, eds., 23 to 48.

percent. That's one penny earned out of every dollar invested. For a biologic this is the root of the $2-3Billion in cost to produce a win. Understandably not all innovators pass the gauntlet, thus the volatility of Biotech stocks.

6. **Pursuit of patent extensions and litigation:** this can be granted through the development of better devices for administering the drug, reduced frequency of dosages and improved packaging. Example: Amgen has gain patent protection on Enbrel in the US until 2029 (approved in 2011 and 2012) even though the innovation occurred in the early 1990's.
7. **Frequency of Patent battles:** Between 2011 and 2014 over 90% of all generics attempting to enter the market faced patent disputes.
8. **Patent Dance required for Biosimilars:**
    a. The FDA tried to limit "Patent Battles" and in theory, shorten the time biosimilars will gain real market entry by requiring what is termed "the patent dance."
    b. The "patent dance" is a complex process by which Sponsors and Biosimilars exchange information resulting in an initial list of patents to be litigated. The process, however, is optional and the decision to institute the dance is controlled by the biosimilar.
    c. The goal of the dance is to resolve patent disputes, facilitate protection for the reference producer when appropriate but also to permit entry by the biosimilar by clarifying the patent situation.
    d. Permitting only reasonable royalties in cases of infringement of patents has the benefit to the biosimilar of reduced damages and long-term litigation costs.
    e. The FDA rule requires that a biosimilar company must exchange submit the entire manufacturing and analytical package to the reference drug producer for evaluation.
    f. This has led to further confusion and legal battles in the marketplace.

Other Challenges & Opportunities:

1. Obtaining patients for clinical trials.
2. Innovators use other tactics beyond patent battles such as offering discounts, developing second generation biologics of reference biologics (called biobetters).
3. **Requirement for Phase IV Studies**: Another challenge is the Post Approval process (better known as Phase IV Clinical studies) which are designed to monitor for side effects that can only become apparent after widespread and prolonged use… that can lead to over $300M in costs.
4. **Costs and Implications:**[35]
    a. 15-25% of all revenue and 30+ percent of all sales dollars goes to the cost of R&D for Pharmaceutical companies.
    b. Governments recognize that R&D is critical towards the development of new drugs that have greatly benefited society as a whole.

[35] "Average Research & Development Costs for Pharmaceutical Companies," Investopedia (Investopedia, August 8, 2019), https://www.investopedia.com/ask/answers/060115/how-much-drug-companys-spending-allocated-research-and-development-average.asp.

   c. Since R&D costs are so high, gross margins tend to be very high for a specific drug during the period of exclusivity (upwards of 86% margins).
   d. This is why governments want to be fair to the innovators and balance that with the need to reduce costs healthcare costs making these drugs more accessible. A tricky balancing act!
   e. For instance, while a super blockbuster drug like Humira (aka Adalimumab, a monoclonal antibody owned by AbbVie) that treats among other things rheumatoid arthritis and Crohn's disease), earned up to $18B in global annual sales only 30% of all drugs clear costs and become profitable.
5. **Need to obtain reference product** for analytical and clinical trials.
6. **FDA Lags in approval:** While they have set a goal of 10 months to review a biosimilar, rejections of any kind have led to much longer periods for approval.
7. **Doctor and Patient Education** will continue to be a challenge for any new biosimilar. Doctors may be smart but don't assume they understand the mechanics of the drugs. I once had an experience with a very successful doctor who didn't know the difference between an active substance and excipient in the drugs he was prescribing.
8. **Commercialization strategies:** Due to lack of harmonization, Biosimilar companies face the challenge of devising different strategies for individual countries and regions.
9. **Discount strategies and reimbursement schemes the trend to drive down costs**
   a. European governments under the EU pay for the majority of healthcare costs and are driving the need to lower costs through the introduction of biosimilars.
   b. In kind, biosimilar companies are offering those countries huge discounts and reimbursement strategies.
   c. Those governments in turn (rather then the health insurance companies in the US) are making decisions which drugs will be prescribed and used "country wide" especially through the "winner takes all" bidding process on national contracts.
10. **Traditional BioPharma becoming Biosimilar players:**
   a. Big Pharma is not sitting back to allow others to "eat their lunch". In addition to aggressive legal strategies, Big Pharma has launched aggressive biosimilar campaigns of their own.
   b. Big Pharma who have developed biologics have a huge learning curve advantage.
   c. They also have funding resources and infrastructure that can accelerate "time-to-market."
   d. Big Pharma increasingly is moving into JVs in manufacturing and licensing (Regeneron and Sanofi).
11. **Enter India**… a tidal wave of research and development to tackle biosimilar opportunities.
12. **China**: The last greatest economic block. Full of opportunity and challenges.

Bibliography

"Average Research & Development Costs for Pharmaceutical Companies." Investopedia. Investopedia, August 8, 2019. https://www.investopedia.com/ask/answers/060115/how-much-drug-companys-spending-allocated-research-and-development-average.asp.

"Biologics & Biosimilars." PhRMA Org. Accessed August 11, 2020. https://www.phrma.org/Advocacy/Research-Development/Biologics-Biosimilars.

Blackstone, Erwin A, and P. Fuhr Joseph. "The Economics of Biosimilars." *Am Health Drug Benefits* 6, no. 8 (2013): 469–78. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/.

"Drug Approvals - From Invention to Market...12 Years!" MedicineNet. Accessed August 11, 2020. https://www.medicinenet.com/script/main/art.asp?articlekey=9877.

FDA § (2018). https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/hatch-waxman-letters.

FDA § (2018). https://www.fda.gov/drugs/generic-drugs/generic-drug-facts.

FDA § (2019). https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda#:~:text=An%20abbreviated%20new%20drug%20application,of%20a%20generic%20drug%20product.&text=To%20be%20approved%20by%20FDA,time%20as%20the%20innovator%20drug.

Gutka, Hiten J., Harry Yang, and Shefali Kakar, eds. *Biosimilars: Regulatory, Clinical, and Biopharmaceutical Development*. 34. Vol. 34. Cham: Springer International Publishing, 2018. https://doi.org/https://doi.org/10.1007/978/-3-319-99680-6.

"Insulin." Wikipedia. Wikimedia Foundation. Accessed August 11, 2020. https://en.wikipedia.org/wiki/Insulin.

Mikulic, Matej. "Global Spending on Medicines 2024 Forecast." Statista, May 25, 2020. https://www.statista.com/statistics/280572/medicine-spending-worldwide/.

Roy, Avik. "Biologic Medicines: The Biggest Driver Of Rising Drug Prices." Forbes. Forbes Magazine, March 8, 2019. https://www.forbes.com/sites/theapothecary/2019/03/08/biologic-medicines-the-biggest-driver-of-rising-drug-prices/.

Schwartz, Rachel. "The Generic Drug Supply Chain." Web log. *Association for Accessible Medicines* (blog). Accessed August 7, 2020. https://accessiblemeds.org/resources/blog/generic-drug-supply-chain.

"Vaccine." In *Merriam-Webster*. Accessed August 11, 2020. https://www.merriam-webster.com/dictionary/vaccine.

Watson, John. "Biosimilars Market To Reach USD 44.56 Billion By Year 2026: Reports And Data." Intrado. "GlobeNewswire", March 19, 2019. https://www.globenewswire.com/news-release/2019/03/19/1757249/0/en/Biosimilars-Market-To-Reach-USD-44-56-Billion-By-Year-2026-Reports-And-Data.html.

"What Are Biosimilars?" Biosimilars Resource Center. Accessed August 11, 2020. https://www.biosimilarsresourcecenter.org/faq/what-are-biosimilars/.

Zhao, Liang, Tian-Hua Ren, and Diane D Wang. "Clinical Pharmacology Considerations in Biologics Development." *Acta Pharmacologica Sinica* 33, no. 11 (2012): 1339–47. https://doi.org/10.1038/aps.2012.51.