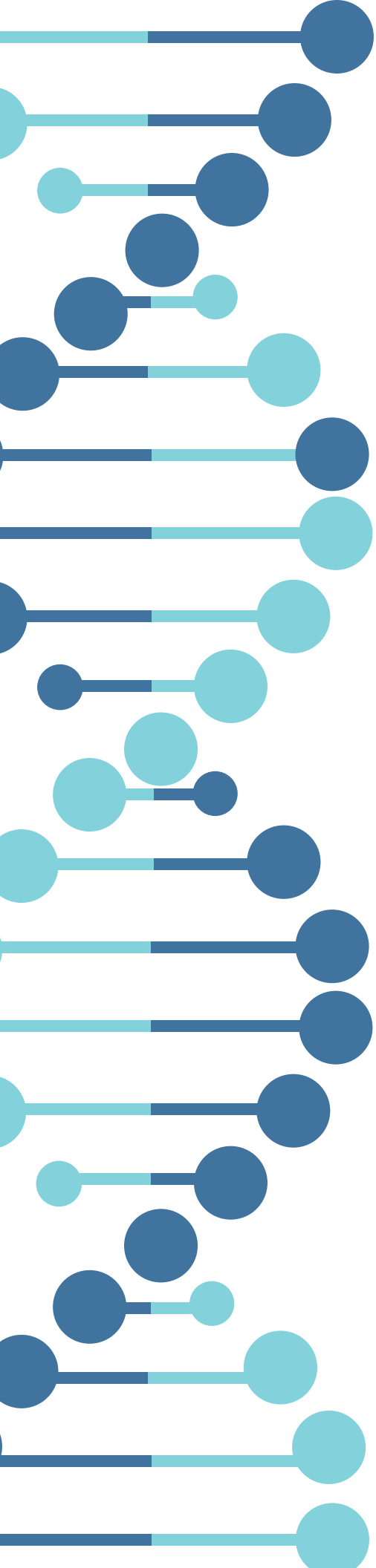

SMALL MOLECULES, BIG IMPACT

Transforming Treatment and Patient Lives

incubate POLICY LAB

Imagine your loved one is diagnosed with a cancer that, up until a few years ago, was only treatable with an hours-long infusion that had to be repeated in a hospital every couple of weeks. Now imagine that same cancer can be treated just as effectively with a pill your family member can take orally, at home, on a set schedule.

The good news is you don't have to imagine. Today, people living with cancer—and many other conditions—can often be treated with medicines that can be picked up at a local pharmacy and taken at home. For decades, dedicated researchers have worked tirelessly to try and find increasingly better ways to deliver drugs into cells in order to treat and cure illnesses. They have made incredible progress, but we still have a long way to go before we cure cancer, end Alzheimer's disease, and discover treatments for the thousands of rare diseases that have no available options. Thankfully, researchers are not giving up and the future is bright—but only if policymakers protect the ecosystem that makes drug discovery possible.

DEFINITIONS OF SMALL AND LARGE MOLECULE MEDICINES

Small Molecule

Small molecule medicines are easily synthesizable chemicals, typically less than one kilogram in molecular weight, enabling them to cross the cell membrane and target intracellular diseases. Small molecule medicines are most often pills but can include formulations like creams or solutions or complex long-acting injectable medicines for diseases such as mental health and HIV. Small-molecule medicines facilitate the success of other treatments, such as organ and stem cell transplants. They are also essential in treating cancer, infections, mental health issues, and neurological conditions. Most medicines are small molecules. Relative to large molecules, small molecules are generally less expensive to manufacture through chemical synthesis, although complex small molecules tend to have a higher manufacturing cost relative to pills. When small molecule medicines lose their exclusive data protection, except in limited circumstances, one or more generic medicines are typically approved. A company seeking approval for a generic small molecule must demonstrate to the FDA that the active ingredients are the same chemical. There is a relatively quick transition to the generic form of the medicine through automatic substitution.[1] That means even if a doctor prescribes the branded

[1] State and federal policy permits automatic substitution for small molecules

form of the small molecule medicine, the person receiving the medicine will get the generic form without asking for it.[2]

Large Molecule

Large molecule medicines are made from organic ingredients such as proteins, cells or nucleic acids (among other biologic-based forms), which allows them to bind to other cells. Biologics include vaccines, blood-derived products, and antibodies.[3] Large-molecule medicines are typically delivered in an intravenous (IV) form. Large-molecule medicines are costlier to take through the research and development process from concept to approval.[4],[5] The manufacturing costs for large molecules are typically more expensive than those for small molecules.[6] When a large molecule medicine loses market exclusivity, a combination of patent protection and regulatory data protection, a similar but not identical medicine may be approved. The same degree of similarity cannot be achieved with biologics as in small molecule chemical synthesis. The "biosimilar" medicine may be prescribed, if specifically requested by the doctor, instead of the original large molecule medicine. The biosimilar is typically not automatically substituted for the original because there are differences between the two molecules.[7]

Cell and gene therapies

Besides small and large molecule medicines, cell and gene therapies have emerged as a promising new modality of treatment. Cell therapies are treatments which use transplanted whole human cells to repair damaged tissue, treat cancer, or treat autoimmune conditions. Stem cells are a unique type of cell which can adapt to take on a new function.[8] Gene therapies are treatments which involve modifying the gene expression of human cells or otherwise change their properties.[9] While the number of approved products of these types are small, their potential to save and change lives is high, curing or drastically improving genetic diseases, and treating cancers more effectively.[10]

2 In some states a health provider can require the brand to be dispensed such as by writing "dispensed as written" on the prescription

3 FDA definition of biologics https://www.fda.gov/files/drugs/published/Biological-Product-Definitions.pdf

4 DiMasi, Joseph and Grabowski, Henry, The Cost of Biopharmaceutical R&D: is Biotech Different? Managerial and Decision Economics, 2007

5 Schlander M, Hernandez-Villafuerte K, Cheng CY, Mestre-Ferrandiz J, Baumann M. How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment. Pharmacoeconomics. 2021;39(11):1243-1269. doi:10.1007/s40273-021-01065-y

6 Gooch et al. from Boston Consulting Group,What Does—and Does Not—Drive Biopharma Cost Performance JULY 07, 2017 accessed https://www.bcg.com/publications/2017/biopharmaceuticals-operations-what-does-and-does-not-drive-biopharma-cost-performance

7 There is a pathway at the FDA for a biosimilar medicine to request interchangeable status with a higher level of evidence than is asked to demonstrate similarity

8 https://www.aabb.org/news-resources/resources/cellular-therapies/facts-about-cellular-therapies/hematopoietic-stem-cells

9 https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products

10 https://www.fda.gov/consumers/consumer-updates/how-gene-therapy-can-cure-or-treat-diseases?%20how%20does%20it%20work?

PHYSICAL DISTINCTIONS FOR SMALL AND LARGE MOLECULE MEDICINES

Getting inside of a cell membrane

Molecules and compounds are constantly moving across the cell membrane, a necessary function of our biology which allows us to circulate materials throughout the body. Water, oxygen, and carbon dioxide, for example, move freely across the cell membrane. Small molecule medicines can penetrate the walls of cells in the body, and can specifically target certain mechanisms inside a cell. Designing small molecule drugs which can efficiently permeate cell membranes has been the subject of many decades of research. Naturally occurring macromolecules like proteins cannot passively diffuse across the cell membrane, and require special channels to cross. Similarly, large molecule drugs require specialized delivery mechanisms to use active transport channels to enter a cell.[11]

One hundred percent of large molecules are unable to cross the blood-brain barrier, and only about 2% of small molecules can.[12] Delivering drugs from the blood to the brain across the blood-brain barrier has been a challenge in medicine development. Moreover, certain small molecules can effectively maintain drug concentration in the brain, which has been a challenge in drug delivery. In medicine, that means that small molecules are used to treat certain conditions, including central nervous system diseases such as Alzheimer's disease, epilepsy, and cancer, among other conditions.[13]

Large-molecule medicines, or biologics, can trigger an immune response in the body. These medicines tend to result in fewer side effects. For example, in auto-immune diseases such as arthritis or graph versus host disease following a transplant, a large-molecule biologic triggers a specific immune response without weakening the entire immune system, as would occur with some small-molecule treatments designed to weaken the entire immune system.[14]

Getting inside of a cell membrane

Small-molecule drugs also have tangible advantages over biologics in their distribution, transportation, and delivery mechanisms. Biologics are typically unstable outside the body, and therefore require cold storage up until a brief period before use. Small-

11 Yang NJ, Hinner MJ. Getting across the cell membrane: an overview for small molecules, peptides, and proteins. Methods Mol Biol. 2015;1266:29-53. doi: 10.1007/978-1-4939-2272-7_3. PMID: 25560066; PMCID: PMC4891184.

12 Pardridge WM. Drug transport across the blood-brain barrier. J Cereb Blood Flow Metab. 2012;32(11):1959-1972. doi:10.1038/jcbfm.2012.126

13 Mikitsh JL, Chacko AM. Pathways for small molecule delivery to the central nervous system across the blood-brain barrier. Perspect Medicin Chem. 2014;6:11-24. Published 2014 Jun 16. doi:10.4137/PMC.S13384

14 Johnston SL. Biologic therapies: what and when? [published correction appears in J Clin Pathol. 2007 Mar;60(3):336]. J Clin Pathol. 2007;60(1):8-17. doi:10.1136/jcp.2005.032300

15 Kay, Jonathan. "Barriers to Biologics Access." AJMC, 18 July 2023, www.ajmc.com/view/barriers-to-biologics-access.

16 Crowley, Joe. "Commentary: A Tweak to the Inflation Reduction Act Could Boost Biotech Innovation." Times Union, 5 May 2023, www.timesunion.com/opinion/article/commentary-tweak-ira-boost-biotech-innovation-18074252.php?IPID=Times-Union-opinion-centerpiece.

molecule drugs come in the form of a pill, syrup, or suspension, while biologics are most commonly injections. Many must be administered with the help of a medical professional, requiring patients to travel to a hospital or clinic to receive their treatment. Small-molecule drugs can be picked up at a local pharmacy and taken at home.[15],[16] This, ultimately, means that biologics may impose a greater burden on patients. In addition to the price of the drug itself, there are expenses associated with time taken off of work, transportation, and childcare if the patient has children.

PROMISING DEVELOPMENTS IN SMALL MOLECULES

Antibiotics

Most antibiotics are small molecules. Developing novel therapies, in addition to appropriate use of antibiotics, will help to address the serious threat posed by antibiotic resistance that results in the death of nearly 5 million people each year.[17] Antibiotic resistance occurs when the bacteria or fungi are not effectively killed by the antibiotic and they evolve and survive resistant to the drug or drugs that were delivered to kill them. Most deaths from antibiotic resistance occurs in low-income countries where small-molecule medicines can be easily transported and stored without infrastructure like refrigeration.[18] Small-molecule medicines are, therefore, essential in solving the antibiotic resistance crisis.

Furthermore, novel approaches to developing new small molecule medicines, including the use of synthetic chemistry and artificial intelligence to screen thousands of potential drug candidate molecules, are yielding potential targeted therapeutics that can cross the bacterial membranes to effectively kill the bacteria. One such study used machine learning to identify promising structures in antibiotics. In lab testing, a class of compounds was found to successfully attack Methicillin-resistant Staphylococcus aureus (MRSA) in mice and obstruct development of antibiotic resistance.[19]

Heart Disease

Small-molecule medicines, including statins and blood pressure-reducing treatments, have contributed to reducing heart disease deaths. It is estimated that 47% of the decline in mortality from cardiovascular disease since 1980 is due to treatments, including drugs and devices.[20] New small-molecule medicines are in development, focused on distinct

17 World Health Organization, 2023

18 ACS Infect. Dis. 2023, 9, 11, 2062–2071

19 Wong, F., Zheng, E.J., Valeri, J.A. et al. Discovery of a structural class of antibiotics with explainable deep learning. Nature 626, 177–185 (2024). https://doi.org/10.1038/s41586-023-06887-8

20 Mensah et al., Decline in Cardiovascular Mortality Possible Causes and Implications, AHA Circulation Research, 2017

21 Alsulami K, Marston S. Small Molecules acting on Myofilaments as Treatments for Heart and Skeletal Muscle Diseases. Int J Mol Sci. 2020 Dec 16;21(24):9599.

22 Lin S, Baumann K, Zhou C, Zhou W, Cuellar AE, Xue H. Trends in Use and Expenditures for Brand-name Statins After Introduction of Generic Statins in the US, 2002-2018. JAMA Netw Open. 2021;4(11):e2135371. doi:10.1001/jamanetworkopen.2021.35371

targets in the heart's fiber muscles to address health risks such as cardiomyopathy.[21] Moreover, many medicines that are used for cardiovascular disease prevention including statins are now mostly generic, providing tremendous benefit to the health system at low cost.[22] Despite multiple therapeutic options for blood pressure control, stroke risk reduction, and cholesterol reduction, some people cannot reach therapeutic goals, and adherence to treatment remains a barrier to better health outcomes. Moreover, heart disease is inequitable in its impact; compared with non-Hispanic white patients, Black people are 30% more likely to suffer from high blood pressure and are 30% more likely to die from heart disease.[23]

Cancer

Multiple Myeloma (MM) remains an incurable disease. However, the five-year survival rate now exceeds 50%. The first medicines to treat MM were corticosteroids and alkylating agents. Newer small molecules complement other biological treatments for MM, such as stem cell transplants and immunomodulating therapies. Recent advances in small-molecule drug development include the use of artificial intelligence to more accurately describe the nuclear pore complex for targeted drug delivery and small-molecule immunomodulation that can be applicable in cancer treatment. Racial disparities in incidence rates for MM should make the development of novel therapies a priority for lawmakers. Black men have an incidence rate 2.1 times that of white men, and Black women have an incidence rate 2.6 times that of white women.[24]

Post Transplant

Even with advances in treatment options, a sizeable portion of people who receive a donated organ experience symptoms of rejection, where the immune system attacks the organ as a foreign object. People who receive an organ transplant are on immunosuppressive drugs for their lifetime after the surgery. If they experience symptoms of rejection, they will have their medication adjusted. Medications given to people who have had a transplant typically include small molecule immunosuppressive drugs. There are health risks associated with long term immunosuppression and new drugs are needed over time to increase survival rates for people who have undergone transplants. Non-white patients receiving heart transplants are almost 3 times more likely to reject the transplanted organ than white patients.[25]

23 Heart disease and African Americans. Office of Minority Health. (n.d.). https://minorityhealth.hhs.gov/heart-disease-and-african-americans

24 Abramson HN. Recent Advances in the Applications of Small Molecules in the Treatment of Multiple Myeloma. Int J Mol Sci. 2023 Jan 31;24(3):2645.

25 Khush, K.K., et al. "Racial disparities after heart transplant: Evidence from image." The Journal of Heart and Lung Transplantation, vol. 32, no. 4, Apr. 2013, https://doi.org/10.1016/j.healun.2013.01.1022.

IMPLICATIONS OF THE POLICY IN THE INFLATION REDUCTION ACT

Small-molecule medicines typically have 13-14 years after FDA approval without a generic competitor. So, by selecting a small-molecule medicine for a maximum fair price at nine years, the IRA significantly reduces the expected revenue for a small molecule relative to that for a large molecule, which will face price-setting after 13 years. It is well established that investment in clinical studies for new and existing medicines is directly related to the expected financial reward. So, by reducing the expected revenue from small molecules to a greater degree than for large molecules, the IRA makes those medicines less attractive investments for clinical development. This distortion in investment away from small molecule technology could be fixed by aligning the Maximum Fair Price setting at 13 years for both small and large molecules.

Reduced and diverted investment in small molecule drugs

As a result of the weakened financial incentive for small-molecule drug research and development, a number of pharmaceutical and biotechnology companies have been forced to cut research into small-molecule drugs. Incubate Coalition's recently launched investment tracker measures the impact of the small molecule penalty on research programs and drug development. As of August 2024, the tracker counts 36 research programs discontinued and 21 drugs discontinued since the passage of the IRA.[26]

As discussed earlier, some of the most promising developments in small-molecule medicines have been in oncology. Cancer drugs disproportionately depend upon post-approval R&D, as this research often elucidates broader use cases for drugs with narrow intended use. The IRA uniquely disincentivizes this late-stage research and therefore has the potential to reduce overall cancer R&D spending by 21.7% compared with pre-2022 levels.[27] This will cause fewer rare cancer drugs to reach market and limit post market study in the drugs that are approved.

Two of the most troubling diversions of investment in oncology, described further in the tracker, are from Pfizer and Roche. Pfizer in early March told investors that the allocation of small molecule drugs in their oncology portfolio will decrease from 94% to 35%. The change, they said, was motivated by the Inflation Reduction Act's price negotiation provisions. Roche discontinued research on two small-molecule drugs for

26 https://lifesciencetracker.com/

27 Philipson, Tomas. "The IRA's Impact on Cancer Patients Is Worse than Predicted." RealClearHealth, 24 Oct. 2023, www.realclearhealth.com/blog/2023/10/24/the_iras_impact_on_cancer_patients_is_worse_than_predicted_988048.html.

28 Manalac, Tristan. "Roche Trims Four Early Assets as Q1 Sales Slip 6% on Currency, Covid Headwinds." BioSpace, BioSpace, 24 Apr. 2024, www.biospace.com/article/roche-trims-four-early-assets-as-q1-earnings-slip-6-percent-on-currency-covid-19-headwinds/.

treating solid tumors in April and discarded molecular candidates for colorectal cancer and psychiatric disorders. Even though their two largest contributors to growth in Q1 of this year were oncology drugs.[28] The diverted investment in promising oncology drugs is a testament to the impact of the IRA.

Jean-François Formela, a partner at Atlas Venture who focuses on novel drug development, said "The difference between nine years and 13 years is a head scratcher… Government needs to be aware that this is impacting the investment decisions of VCs and small biotechs."[29]

Conclusions

The distinction in the IRA between small-molecule medicines and biologics in policy is, in reality, a legacy of a time when biologics were novel. The technological and economic landscape of the time required such a codification within the law to balance the incentives for firms developing different types of drugs. The biopharmaceutical landscape has since shifted, distorting the incentives laid out for developing small-molecule medicines versus biologics. The provisions within the IRA have resulted in investment being diverted from research into life-saving drugs. Ultimately, the IRA is a threat to patients and future health.

In February of this year, Congressmen Greg Murphy, Don Davis, and Brett Guthrie introduced the Ensuring Pathways to Innovative Cures (EPIC) Act. This legislation would diffuse the harmful text of the IRA and restore research and development incentives for small-molecule drugs. Fixing the IRA should be a priority. Arbitrary policy based on outdated economics should not deter promising science. Revising the IRA to extend the time to 13 years before prices set by the federal government for small-molecules will not only save innovation in small-molecule medicines, but it will also save lives.

Kirsten Axelsen writes for the Incubate Policy Lab. She is a biopharma industry veteran who consults with life sciences companies as a policy advisor. Kirsten is an economist, not a lawyer and is a Policy Advisor to DLA Piper.

29 Weisman, Robert. "Biotech Investors Push to Extend Time before Pills Are Subject to Price Negotiations - The Boston Globe." BostonGlobe.Com, The Boston Globe, 19 Oct. 2023, www.bostonglobe.com/2023/10/17/business/biotech-investors-pills-price-negotiations/.