



## Drug Policy 101: Breaking Down Different Types of Drug Products

Pharmaceutical companies continue to raise prices to unaffordable levels, forcing patients and families to choose between paying their rent or mortgage, or paying for their medication. From congressional hearings to expansive media coverage, there is unprecedented attention on how much Americans pay for drugs. Experts have cited patent abuses, lack of competition, and the failure of U.S. policies to meaningfully constrain the pharmaceutical industry's pricing power among the reasons for excessively high prices.

This paper seeks to explain differences between the basic types of drugs. While there is significant variation within each of the broad categories, knowing the differences between the basic types of drugs can shed light on market dynamics, the competitive environment, and other factors that contribute to manufacturers' drug pricing decisions.

### Types of drug therapies

There are considerable and important differences between the more traditional small-molecule drugs that we are most familiar with and new and innovative therapies derived from living organisms. Understanding how different therapies function, how they are made, and how they are approved and regulated is crucial to the larger pricing conversation.

Most drug therapies fall under one of the following categories: small-molecule products, biologics, and cellular and gene therapies. Innovations within these categories have led to a recent rise in new treatment types, including immunotherapy.

**Small-molecule drugs:** Small-molecule medications are made from chemical compounds and represent the vast majority of drugs on the market. These drugs, typically in tablet or capsule form, can easily reach their intended destination in the human body due to their size. Traditional small-molecule drugs

are regulated by the U.S. Food and Drug Administration's Center for Drug Evaluation and Research (CDER) through the New Drug Application process, under authority of the Federal Food, Drug and Cosmetics Act (FD&C).<sup>1</sup>

Small-molecule drugs are typically much easier to manufacture than other types of therapies because they are synthesized through established processes resulting in the same chemical compound. This enables generic manufacturers to make exact replicas of the brand-name drug at a relatively low cost. The easier manufacturing process for small-molecule drugs has contributed to more robust competition than for other types of drug products. Nevertheless, small-molecule drugs may still come at high prices.

Generic versions of traditional small-molecule drugs must be "bioequivalent" – or essentially identical – to the brand-name drug, also referred to as the innovator product. To receive approval and enter the market to compete with the branded drug, generic drugs go through a faster review under the Abbreviated New Drug Application process created by the Hatch Waxman Act of 1984.<sup>2</sup> Due to the expedited ANDA process, generic drugs now account for about 90% of all prescriptions in the United States.<sup>3</sup> Generic drugs, like their branded equivalents, are regulated by the FDA under the FD&C Act.

#### Examples of small-molecule drugs

- Advil (ibuprofen) is a non-steroidal anti-inflammatory drug (NSAID) used to treat mild pain, fever and headaches.
- Sovaldi (sofosbuvir) is a higher-priced example used to treat hepatitis C.

#### Example of a generic small-molecule drug

- Ibuprofen, which is the active ingredient in Advil, is used to treat mild pain, fever and headaches.

**Biologics:** Biologics, derived from living organisms, are large-molecule – approximately 1,000 times larger than small-molecule – drugs based on proteins. Biologics are often used to treat complex, chronic, and rare diseases. They may require a prescription by a specialist, special handling, intravenous administration, and a high degree of patient management to ensure compliance and safety.

Biologics, which treat conditions such as anemia, diabetes, multiple sclerosis, hepatitis, and cancer, are the fastest growing class of therapies in the United States.<sup>4</sup> Making up just 2% of all prescriptions, they account for 40% of U.S. pharmaceutical sales and 70% of the growth in drug spending.<sup>5,6</sup> Biologics are regulated by the FDA's CDER and the Center for Biologic Evaluation and Research under authority of the Public Health Service Act.<sup>7</sup>

Biosimilars are highly similar variants of already approved "reference" biologic drugs that show no meaningful clinical difference in terms of safety, purity, and potency.<sup>9</sup> In contrast to small-molecule generic drugs, it is impossible to produce a biosimilar that is identical to its reference product: batch-to-batch variability among biologic drugs prevents exact replication. The FDA therefore requires biosimilar manufacturers to meet more rigorous standards than for small-molecule drugs to establish "biosimilarity" or "interchangeability" to the original product. To be deemed interchangeable, the biosimilar and original products must produce the same clinical result, and switching between the different products results in no additional risks in terms of safety or efficacy.<sup>10</sup> Products deemed interchangeable may be substituted by a pharmacist without intervention of the prescriber, similar to how generics are dispensed.

#### Examples of biologics

- Humira (adalimumab), which is used to treat rheumatoid arthritis and Crohn's disease, among others, is the nation's best-selling drug by revenue.<sup>8</sup>
- Neupogen (filgrastim) is used to treat infections for patients with a low white blood cell count due to cancer medicine.
- Opdivo (nivolumab) is an immuno-oncology drug approved for treatment of certain types of lung cancers.

Biosimilars are a relatively new phenomenon. The pathway for biosimilar approval – Abbreviated Biologics License Applications – was passed into law in 2010 under the Biologics Price Competition and Innovation Act. Thus, the biosimilar market in the United States is still struggling to gain a foothold, especially with over-patenting of reference biologics creating barriers to competition. Of the 21 biosimilars approved by the FDA,<sup>11</sup> only 7 are on the market<sup>12</sup> and none are deemed interchangeable.

#### Examples of biosimilars

- Zarxio (filgrastim), a biosimilar to brand-name biologic Neupogen and the first biosimilar approved by the FDA, is used to reduce the risk of infections in cancer patients who might be immunocompromised.<sup>12,13</sup>
- Inflectra (infliximab), a biosimilar to brand-name biologic Remicade, is used to treat rheumatoid arthritis and Crohn's disease, among others.

Biologics are often significantly more complex to manufacture than small-molecule drugs. Due to their size and complexity, specialized manufacturing processes are often necessary and involve large molecule mixtures that are harder to control. Thus, the manufacturing process itself can influence how the biologic performs, and it is virtually impossible for a biosimilar manufacturer to produce an identical version of the drug. As a result, manufacturing biosimilars is more expensive and complicated than manufacturing small-molecule generics.

#### Specialty drugs

Specialty drugs have no formal definition, and each health plan has a different specialty drug list. They are typically used to treat complex, chronic, and often rare diseases, and are often complex to administer or require special handling. They are often biologics, but there are also many small-molecule specialty drugs. Specialty drugs usually have very high prices.

**Cellular and gene therapy:** This category of therapies include cell transfer and gene modification or manipulation drugs, used to treat cancer, genetic diseases, and infectious diseases.<sup>15</sup> Cellular and gene therapy products are biological products regulated by the FDA's CDER.<sup>16</sup> Often in a single dose, gene therapies aim to fix the root

causes of disease by replacing a disease-causing gene with a healthy copy of the gene, inactivating a disease-causing gene, or introducing a new or modified gene into the body.<sup>17</sup> Gene therapies accomplish this using “vectors” that replace, add, or turn off genes directly in cells. As a result, some of these drugs have curative potential for certain patients. But information is needed to see if these therapies offer long-term benefit since most of these therapies were approved based on relatively small clinical trials with limited time for analysis.

The world is only just now entering the era of gene therapy innovation, with the first major FDA approvals occurring over the past few years. Only 17 cellular and gene therapies are on the market today.<sup>18</sup> However, hundreds of these products are currently in development and up to 20 products could be approved each year by 2025, according to the FDA.<sup>19</sup> Most of the new cellular and gene therapies are targeted at oncology conditions.

While gene therapies often constitute major medical breakthroughs, they also tend to have extremely high prices. High prices for gene therapies are often justified based on the drugs’ curative potential, even though maintenance therapy and multiple doses may ultimately be required for many patients.

Administration of cell and gene therapies can also be relatively involved, significantly adding to the overall cost of these already astoundingly high-priced therapies. For example, chimeric antigen receptor T-cell (CAR-T cell) therapies, where a patient’s T-cells (a type of immune system cell) are modified to selectively kill cancer cells,<sup>20</sup> require extraction of a patients’ own cells, genetic modification, and reinfusion of the new cells.<sup>21</sup> Because many of these therapies are intended to have long-term effects,

#### Examples of gene therapies

- Zolgensma, a breakthrough gene therapy treatment for infants with spinal muscular atrophy. Priced at \$2.1 million, Zolgensma is now the highest-priced drug in the world.
- Kymriah (tisagenlecleucel), the first gene therapy approved by the FDA, is a CAR T-cell therapy for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia.<sup>22</sup>

#### Immunotherapy

Immunotherapy treatments, which can be a form of biologic, cellular, and gene therapy, strengthen the ability of the immune system to detect and destroy diseases including cancer.<sup>23</sup> CAR-T cell therapy – Kymriah, for example – is one immunotherapy treatment gaining attention.<sup>24</sup> Checkpoint inhibitors are another type of immunotherapy that are quickly growing in use to treat cancer. An example is Opdivo, the biologic drug mentioned above, approved to treat various types of cancers.

#### Vaccines

Vaccines stimulate the immune system to produce immunity to a specific disease.<sup>25</sup> Vaccines cause the body’s immune system to recognize and destroy a tumor or microorganisms such as bacteria or viruses.<sup>26</sup> Vaccines are responsible for reducing preventable infectious diseases such as measles and pertussis to an all-time low, and also protect us from common illnesses today such as influenza and HPV, a virus which can cause cancer later in life. Some vaccines act as cancer treatment designed to help the immune system slow disease progression and kill cancer cells that have already developed in the body. These vaccines are typically made from a patient’s own tumor cells or from substances taken from tumor cells.<sup>27</sup> Vaccines are regulated by the FDA’s CBER.

they are raising new and challenging questions about drug prices and how to finance the cost of these products over the course of a patient’s life.

## Conclusion

As patients, providers, and health systems continue to grapple with unsustainably high drug prices in the United States, it is important for policymakers to understand the distinct differences between broad categories of therapies as they examine potential solutions. The nuance of how therapies are developed, administered, and regulated sheds light on the unique market dynamics of each type of drug. Simply put, there is no one-size-fits-all pricing solution, but knowing these distinctions can help shape the future of drug pricing policy.

## End Notes

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