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Prescription Drug Competition Hampered by Policies, Barriers and Delay Tactics

The U.S. prescription drug market is complex and, for a variety of reasons, lacks the competitive forces found in other sectors of our economy that can help regulate prices. This overview explains the steps involved in bringing a drug to market and the various policies and practices that, for both intended and unintended reasons, reduce competition in the marketplace.

Getting to Approval

Preclinical Phase (1-3 years)

The preclinical phase is when the drug is first being developed and tested. Three things happen during this phase:

- Drug development: Drug sponsors—companies and research institutions—develop a new drug compound with the hope of having it approved by Food and Drug Administration (FDA) for sale in the United States.
- Animal Testing: The sponsor tests the new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being researched.
- An investigational new drug (IND) application: The sponsor submits an IND application to FDA based on the results from the initial animal testing. The application must contain a plan for testing the drug on humans.

The FDA reviews the IND to ensure that the clinical trials will not place human subjects at risk of harm. The FDA also verifies there will be informed consent and human subject protection.

Clinical Trials Phase (2-10 years)

The clinical trials phase is divided into three parts.

- *Phase 1:* This phase emphasizes safety and seeks to determine the drug's most common side effects, the frequency of the side effects and how the drug is metabolized. These trials usually use about 20-80 volunteers.
- *Phase 2:* This phase emphasizes effectiveness. The goal is to obtain data on whether the drug works on people who have certain diseases or conditions compared to a placebo group. These trials usually use hundreds of volunteers.
- *Phase 3:* This phase focuses on gathering information about safety and effectiveness, studying different populations and dosages and using the drug in combination with other drugs. These trials usually have thousands of volunteers.

Patent Protection (20 years)

Generally, the term of a new patent is 20 years from the date the patent application was filed in the United States. A company may apply for a patent from the U.S. Patent and Trademark Office during the clinical phases of a drug

and can include a wide range of claims. Patent information is expected to be finalized and submitted with the NDA application prior to approval. Because patents are usually filed while drugs are still in testing, the clock starts long before the drug goes on sale. Typically, new drugs ready for sale end up with a remaining patent monopoly of roughly 12 years.

New Drug Application (about 1 year)

After the clinical trials are complete, the sponsors complete a New Drug Application (NDA) asking the FDA to approve the drug for marketing. The NDA includes all data from the animal and human trials that reveals how the drug interacts with the body. The FDA has 60 days to decide whether to conduct further review, and if so, the agency has 10 months to approve the drug (6 months for priority drugs). The FDA also reviews the labeling of the drug to make sure proper information is communicated to healthcare professionals and consumers. The FDA will then do a final inspection of the facilities where the drug will be produced and either approves or disapproves the drug.

Risk Evaluation and Mitigation

The FDA Amendments Act of 2007 gave the FDA authority to optionally require a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of certain prescription drugs outweigh their risks. If information comes to light regarding the risk of serious adverse events associated with the drug, the FDA can require the manufacturer use risk mitigation strategies beyond FDA-approved professional labeling. As part of a REMS, a drug manufacturer may be required to provide certain information to patients and healthcare providers or to restrict a drug's sale and distribution. A REMS can be required before or after a drug is approved.

After Drug Approval

Post-Marketing Phase

Usually, post-marketing trials are not required, but sometimes the FDA may require the sponsor to do additional studies after a drug enters the market to examine a safety concern. This phase is to detect or investigate any serious, unexpected adverse effects that might not have come to light during the clinical trials. The sponsor is required to submit periodic safety updates to the FDA. Physicians and consumers can report adverse effects of the drug, which in some cases can lead to a drug's removal from the market.

Patent Extenders

There are multiple tactics used by manufacturers to extend the term of their patent. The most common is to create Me-Too Drugs. Me-Too Drugs are very similar to first-in-class drugs. The benefits of Me-Too-Drugs are minimal as the formulations are relatively the same. They are characterized by:

- Minor changes in dosing.
- Prolonged-action preparations (controlled-release, sustained-release, extended-release, long-acting).
- Fixed-dose combinations: two or more drugs in one pill. Even if both drugs are off patent, a new patent can be obtained for the combination.
- Develop metabolites, prodrugs, analogs or enantiomers, most of which have no advantages over the originator drug. Enantiomers are molecules that are mirror images of each other, so it has become common practice to introduce a drug as a mixture of enantiomers. This allows the company to release the active enantiomer as a "new, improved" product when the patent is close to expiring, even though the formulation stays the same.

Pharmaceutical manufacturers spent more than $107 million promoting the use of just 20 Me-Too Drugs in the last five months of 2013.

Example: Pitavastatin, the eighth statin approved for use in the U.S., received FDA approval eight years after generic lovastatin was approved and four years after two additional statins—pravastatin and simvastatin—lost patent protection and generic versions entered the market.

Market Exclusivity (6 months–7 years)

Exclusive marketing rights are granted by the FDA upon approval of a drug. Exclusivity is not added to the patent life—it may run concurrently or it may extend the period of protection from competitor drugs. The policy

was designed to promote a balance between new drug innovation and generic drug competition.

There are four types of market exclusivity that drugs can fall under:

Orphan Drug Exclusivity (7 years): Granted to drugs designated and approved to treat diseases or conditions affecting fewer than 200,000 people in the U.S. (or more than 200,000 with no hope of recovering manufacturing costs). More than 50 percent of new drugs are approved for orphan populations, and more than half of orphan approvals are first-in-class, indicating that no other treatment exists for the approved indication.

New Chemical Exclusivity (5 years): The Hatch-Waxman Act established a five-year exclusivity that is available to drugs that qualify as a new chemical entity (NCE). The purpose of this is to encourage the development of innovative drug products that include an entirely new active ingredient (active moiety), in contrast to me-too drugs that incorporate chemical variants of previously known compounds. During the five-year period of NCE exclusivity, the FDA may not accept a generic drug company's application to market a drug product containing the same active moiety protected under the NCE exclusivity.

"Other" Exclusivity (3 years): Granted to drugs when the application or supplement contains reports of new clinical investigations that are conducted or sponsored by the applicant and essential for further approval.

Pediatric Exclusivity (6 months): Unlike the other types of exclusivity, pediatric exclusivity can grant an additional six months of market protection at the end of listed patents and/or exclusivity for sponsor's drug products containing the active portion, when the sponsor has conducted and submitted pediatric studies on the active portion in response to a written request from the FDA.

There is also a type of exclusivity tailored to generic drugs. The FDA may grant exclusivity to ***abbreviated new drug applications*** **(ANDAs)** for generic drugs. Under the Drug Price Competition and Patent Term Restoration Act—or the Hatch-Waxman Act—a company can seek approval from the FDA to market a generic drug before the expiration of the patent of the brand name drug upon which the generic is based. The first company to submit an ANDA with the FDA has the exclusive right to market the generic drug for 180 days.

Pay for Delay

Branded drug manufacturers have been able to sidestep competition by offering patent settlements that pay generic companies not to bring lower-cost alternatives to market. These "pay-for-delay" patent settlements effectively block all other generic drug competition for a growing number of branded drugs. According to a Federal Trade Commission study, these anticompetitive deals cost consumers and taxpayers $3.5 billion in higher drug costs every year.

Example: A generic version of the drug Provigil, prescribed for sleep disorders and multiple sclerosis-related fatigue, was expected to go on the market in late 2005. But brand-name manufacturer Cephalon paid more than $200 million to four different generic drug manufacturers, who kept their generics off the market until 2012. In the meantime, many patients had to pay up to $1,200 each month for the branded drug, or manage without it.

Abuse of REMS Requirements

As described above, the FDA can require a Risk Evaluation and Mitigation Strategy, which are management plans to ensure that the benefits of certain prescription drugs outweigh their risk.

Drug manufacturers have recently exploited REMS as a tool to deter generic entry. Depending on the level of risk associated with a product, a REMS program can require restricted distribution of a drug, but brand drug firms have been accused of using this requirement to deny generic manufacturers access to drug samples. Generic manufactures need these samples in order to successfully complete an ANDA, which is required for FDA approval. Estimates suggest that REMS abuse could cost consumers $5.4 billion annually.

Abuse of Orphan Drug Status

The Orphan Drug Act of 1983 was passed to encourage drug manufacturers to create drugs for markets too small to be profitable, particularly for diseases that affect few people. As described above, the FDA can award extra years of market exclusivity to these so-called "orphan

drugs," along with other financial benefits and easier regulatory treatment. For example, in 2012 one of the biggest orphan drug companies, BioMarin, received $32.6 million from a combination of federal and state of California tax credits.

Finding new uses for existing drugs does have scientific and patient benefits but the system is being abused. Manufacturers can take an existing drug which has already benefited from patent protection and market exclusivity, run a clinical trial on a small off-label use, prove effectiveness, gain orphan status, and raise prices for consumers significantly due to lack of competitors. Manufacturers can also be relieved from the requirement to sell orphan drugs at a discount to hospitals and clinics serving lower-income communities. More than 200 companies have brought almost 450 so-called orphan drugs to market since the law took effect.

Examples: Humira is the best-selling arthritis medicine in the world, but has gained orphan drug status for treatment of pediatric Crohn's disease. In 2016, there was a 9.9 percent price increase. Ten years ago, a Humira pen injector with two syringes sold for $1,258. Today it costs $4,441.

Another drug, 3,4-diaminopryne, used to treat rare neuromuscular diseases for over thirty years, recently gained orphan drug status in the EU, causing its price to rise from $1,600 to $60,000 per year.

Regulatory Backlog

There is a large backlog of generic drugs awaiting U.S. regulatory approval, which means that for some off-patent drugs, either none or few generic versions have been approved. This backlog curtails drug competition.

The number of Abbreviated New Drug Applications currently under review at the FDA is approximately 2,350, while the number of ANDAs awaiting industry action is approximately 1,850.

Small Patient Population

Certain brand-name drugs treat conditions too rare to attract multiple manufacturers and this leaves the sole maker with a monopoly unrelated to patent and FDA rules. Many new drugs are for rare conditions or cancer subtypes involving a particular genetic mutation, so they might help just thousands or hundreds of patients.

Example: Daraprim is a 62-year-old drug that treats toxoplasmosis, a parasitic infection that can affect those living with HIV/AIDS and cancer. Turing Pharmaceuticals drastically increased the price of this life-saving drug from $13.50 to $750 per pill—a stunning 55-fold overnight increase. Daraprim's patent and period of market exclusivity has expired but the small patient population meant that no one stepped in to create a generic competitor. As a result, Daraprim was the only game in town.

Competitors Exist but Price Rises Anyway

Even if a drug has two or three different manufacturers, price increases can still occur via shadow pricing. For example, the price of Gleevec, a Leukemia cancer drug developed by Novartis increased from $26,400 for a year's supply in 2001 to $120,000 in 2016. The price jump occurred because Bristol-Myers Squibb introduced a drug called Sprycel that entered the market at a higher price, which enabled Novartis to increase the price of Gleevec to catch up.

Abuse of Citizen Petitions

Citizen petitions enable consumers to voice their concerns about drugs to the FDA. But a majority of citizen petitions are instigated by pharmaceutical companies themselves—as a way of fighting off a competitor's cheaper generic drug.

For example, between 2006 and 2012, ViroPharma filed 24 citizen petitions with the FDA to delay the approval of generic versions of Vancocin, an antibiotic. That was in addition to its 18 public comments, a new drug application supplement, and three lawsuits against the FDA.

In 2016, brand-name companies filed 92 percent of citizen petitions. However, the FDA is aware of the problem and is now rejecting citizen petitions filed by those companies.

Discussion

Consumers and policymakers are concerned about rising drug costs. Policymakers are searching for solutions, including increased competition in the market place. Lack of competition drives up costs for consumers yet also reflects very real policy tradeoffs intended to reward drug innovators with a period of monopoly protection in return for bringing valuable products to market.

As this overview shows, there are opportunities to rein in abuses and promote competition. Promising policy approaches designed to increase competition include:

- Addressing FDA's backlog and streamlining the application process
- Amend the Orphan Drug Act
- Prevent Pay for Delay tactics
- Enforce Risk Evaluation and Mitigation Strategy guidelines
- Modify patent rules to increase market competition

For reasons described above, addressing abuses will help but not fully address escalating drug prices. There will also be drugs for which competition is not an immediate option (in a period of legitimate patient protection, small patient population, etc.). Furthermore, as the Gleevac example demonstrates, competition does not always mean lower prices. In some cases, manufacturers of branded drugs raise prices in response to new branded competitors. In these cases, policymakers will need to look to a different set of remedies to address high prices.

Note: Citations to the evidence can be found on our website at *www.healthcarevaluehub.org/Rx-Competition*

Sunita Krishnan, Hub research assistant, authored this report.

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