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The proposed Affordable Drug Manufacturing Act: Friend or foe for biosimilars?

Ha Kung Wong and April Breyer Menon of Venable discuss how high barriers to biosimilar market entry may make government development and manufacturing challenging.

Biosimilars, biological products highly similar to and without clinically meaningful differences from an existing FDA-approved biologic, are finally on the rise. In fact, of the 16 approved U.S. biosimilars, 12 were approved in 2017 and 2018. Additionally, four biosimilars launched in the last six months, which is as many as were launched in 2015 through 2017 combined.

The recent 2018 FDA Biosimilars Action Plan, laying out initiatives meant to increase research, development, and approval of biosimilars, demonstrates the government's commitment to growing biosimilar development. However, at the same time, there is continued concern about rising drug prices, which the government is eager to address.

Generic drug manufacturers recently came under fire pursuant to state antitrust suits alleging that a "cartel" of 16 generic manufacturers conspired to fix prices on more than 300 drugs. This attracted Senator Elizabeth Warren's attention, leading to proposed new legislation authorizing public manufacture of generic drugs wherever drug companies manipulate markets to drive up prices.

This new legislation, the Affordable Drug Manufacturing Act (ADMA), establishes an Office of Drug Manufacturing that would be required to manufacture at least 15 different generic drugs in its first year where the FDA determines there is a failure in the market. This allows the U.S. government to manufacture generic versions of drugs "in cases in which no company is manufacturing a drug, when only one or two companies manufacture a drug and its price has spiked, when the drug is in shortage, or when a medicine listed as essential by the World Health

Organization faces limited competition and high prices." While generally addressing off-patent drugs, Warren's bill also allows the government to buy or compulsorily license patents to manufacture the generic versions itself, or through contracts with other manufacturers, and then sell them at a "fair price."

Many have wondered how this bill could impact the growing field of biologics and biosimilars. While there are similarities between small-molecule generic and biosimilar markets, there are many differences requiring consideration when analyzing the impact of the ADMA on biosimilars. Primarily, the differences in development and manufacturing complexity, costs, uncertainty, and time to market entry will make government manufacture of biosimilars more difficult and could impact company incentives to entering the biosimilar market more severely than in the generics market.

Feasibility of the ADMA for biosimilars

The current ADMA mainly focuses on manufacturing and is not clear regarding whether the government plans to develop its own biosimilars, or to obtain rights through purchase or compulsory licensing, but it does not directly consider the unique developmental and marketing hurdles that could impact the feasibility of government manufacture of biosimilars.

• Development

Biologics and biosimilars are more complex than small-molecule drugs, as they are bigger, have greater structural complexity, and are made in living cells as opposed to through chemical synthesis. This makes biosimilars harder and more time consuming to develop. According to the Federal Trade Commission, biosimilar development can take eight to ten years, compared to three to five years for small-molecule generics.

Biosimilar drugs are similar to their reference products, not exact copies like small-molecule generics. Attempts at making biosimilars are riskier for companies and the government because of their complexity, as there is no certainty a product in development will actually be safe and effective in patients.

Résumés

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• Manufacture

Generally, biologics and biosimilars have more complex manufacturing procedures and more stringent manufacturing requirements than traditional generics, which has limited the companies capable of manufacturing biosimilars and created a high barrier to entry. Many biologics require unique processes and manufacturing machinery, meaning the government would have to provide multiple unique facilities potentially limited to producing a single biosimilar. Providing adequate, FDA-approved manufacturing facilities could significantly burden the government, and impact manufacturing efficiencies.

• Approval

Clinical testing required for biosimilars is more extensive than for traditional generics, because of the increased trials necessary for demonstrating biosimilarity compared to showing bioequivalence

for small-molecule generics. This increases development cost, time for biosimilar approval, and administrative burden on the government, because it would need to conduct its own clinical trials adequate for FDA approval.

In addition, because of their complexity, there is a higher probability of development failure in clinical trials, meaning an approvable biosimilar may never be produced, despite investment in research and clinical trials.

• Marketing

While small-molecule generics are automatically substitutable at the pharmacy, biosimilars are not. This means biosimilar manufacturers face marketing costs, much like innovators. The ADMA currently doesn't consider the marketing burden that would be placed on the government to have doctors prescribe its drugs.

The government could avoid these costs by developing automatically substitutable, interchangeable drugs, which have more extensive clinical testing showing they can be switched with the biologic reference product and are expected to produce the same clinical result as the reference product in any patient. But this development would increase time and cost, not to mention the uncertainty surrounding interchangeable status approval, as an interchangeable has yet to be approved in the U.S.

• Cost

The Federal Trade Commission estimated biosimilar development cost at approximately \$100-200 million, significantly more than the \$3-5 million estimate for a small-molecule generic. The resources required for this process may end up outweighing any potential benefit from increased accessibility and reduced patient cost, as the government cost is sure to come in part from taxes collected from the very patients it seeks to benefit. This may also impact the government's ability to significantly reduce the cost of the biologic, at least in the short term, as presumably it would need to recuperate its investment to continue developing other drugs.

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• Change in circumstances during development

Potential changes in the state of the biosimilar market during the lengthy development time also need consideration. If one ADMA condition was met, it could take years before the government would have a drug it could bring to the market. Because of that lapse in time, the market could look very different, to the point where government intervention would no longer be necessary, i.e., there may no longer be a drug shortage, more competitors may have entered the market, or the price may have changed.

• Biosimilar uptake

Yet another consideration is uptake of biosimilars in the market. Currently, most biosimilars hold a small U.S. market share compared to the reference products, despite costing less. Therefore, the fact that the government produces a lower-cost biosimilar doesn't mean that prescriptions will significantly shift from reference products. This could limit the cost-reducing impact of government biosimilar manufacture.

These unique challenges should be fully addressed before the government begins creating or manufacturing its own biosimilars.

Potential impact of the ADMA on the biosimilars market

Assuming all the feasibility concerns for government biosimilar development and manufacture could be overcome, what are the possible impacts of government entry into the biosimilar market?

It's important to note that, as detailed above, the proposed ADMA is limited to specific situations, so it's possible this proposed act won't impact the biosimilars sector at all, as there's no indication that any of the requirements would be met for any potential biologic product. But if passed, the possibility of government competition or compulsory licensing could stifle competition by reducing the number of Abbreviated Biologics License Applications filed.

The current stage of the biosimilar market in comparison to the small-molecule generic drug market should be considered, as the size difference is staggering. The U.S. biosimilars market consists of only 16 approved biosimilars, and only 7 of these drugs are currently being sold. In contrast, the FDA approved or tentatively approved 971 generic drugs in FY 2018 alone. Adding the government as a potential competitor to the small biosimilars market is likely to impact company decisions to enter the market.

If there is a possibility of the government becoming a competitor and pricing drugs at a much lower price, or the government taking a compulsory license for only "reasonable" compensation, the economic incentive to entering the market is likely to decrease. At the least, the uncertainty and lower potential return on investment will create yet



another hurdle to private company entrance into the biosimilar market. At the extreme, profit margins could become so slim and uncertainty of government intervention so high, that no companies would be willing to produce biosimilars, and the government may face having to develop its own biosimilars of all the biologics to lower costs. This could ultimately reduce accessibility of biologic products to patients instead of increasing it.

Another concern is how a "fair price" will be determined. Although drugs should be available to patients who require them, the U.S. pharmaceutical market has traditionally been based on demand and recoupment of investment, making it possible to invest in developing the next drug. Having the government dictate a "fair price" may negatively impact companies' ability to properly recoup invested resources, thus making entry into the market less attractive. Thus, the uncertainty of what the "fair price" will be could negatively impact a company's decision to enter the market, making investment too risky.

In addition to potentially decreasing biosimilar development and applications, the possibility of government intervention prior to patent expiration, such as through compulsory licenses, particularly for drugs listed as essential by the World Health Organization, or facing a shortage, may concern innovator companies and decrease their willingness to invest in researching and developing new drugs, for fear they would be unable to recoup their investment. Providing increased patient access to biosimilars is an important goal but should not be pursued at the expense of biologic or biosimilar development in the first place.

Conclusion

The proposed ADMA has a long way to go before it's enacted, assuming it's enacted at all. And during this congressional process, many elements of the ADMA may change.

Regardless, one thing is for sure; patients require access to important life-saving medications, and the government has some responsibility to ensure there are no undue restrictions to this access. But the solution will require much more thought, as obtaining access at the expense of research and development is unlikely to be in the patient's best interests.

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