FDA to ‘usher in a new era of competition for biosimilars’

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Statement from FDA Commissioner Scott Gottlieb, M.D., on new actions advancing the agency’s biosimilars policy framework

Our public health obligations touch on many aspects of how medical products are developed and used by patients and providers.

The bedrock of our mission is our consumer protection role — our obligation to protect patient safety. Part of our mission also inspires us to promote beneficial innovations that can advance patient care. And along the way, as we pursue these twin goals, we also take steps to inspire competition that can help lower costs and broaden patient access.

As competition increases — and costs fall — more patients can afford to access important medical advances. We can promote access without lowering incentives to innovate. We can help keep the rise in medical spending on a sustainable path for public and private health plans.

This has been especially true when it comes to new drugs.

So we’re focused on what steps we can take to maintain balance through transparent, predictable and efficient regulatory processes for both innovative drug products and generic drugs approved through abridged pathways like an Abbreviated New Drug Application, or ANDA.

Timely and efficient regulatory processes ensure that the U.S. remains a driving force in global biomedical innovation. A robust pathway for generic entry after patents and other exclusivities have lapsed means that our market is one of the most competitive generic markets in the world. This helps balance the best of both opportunities for patients — timely access to the newest and potentially most beneficial medical breakthroughs; and immense value once the patents and exclusivities that incentivized the investments in those innovations have lapsed.

In recent years, we’ve been seeing progress on both fronts.

In 2011, we set a record for the greatest number of generic approvals ever in a single year. We

broke that record for the 2018 fiscal year. And we'll come close to breaking it again for the whole 2018 calendar year.

And when it comes to novel drugs, we've already broken by a large margin all previous records, and the year's not over yet. What's more, some of those previous records were set in years when there were a lot of drugs that critics bemoaned were me-too medicines — novel chemical entities that all addressed the same common, therapeutic targets.

The kinds of innovation we're seeing now are more targeted, more fashioned against significant medical needs, and far more effective.

The competition from generics helps drive this innovation, by compelling life science companies and their investors to back new technology as a way to sustain the high margins that have helped fuel investment in these endeavors. It's one reason why the life science industry realizes one of the highest rates of investment in research and development — almost 19 percent of revenues, on average.

The result of this progress is that we openly talk about curing cancers that were recently fatal, or inherited pediatric diseases and blood disorders that often obligated children to lives of suffering and lives cut short. Such talk would have seemed irresponsible a decade ago. Today, there are conferences devoted to the realization of these opportunities. And when it comes to the other end of the continuum that spans innovation and access, generic drugs account for about 90 percent of all retail scripts; saving patients about $1 trillion over the previous decade.

But not all parts of the pharmaceutical market have been equally open to competition from more affordable products. This is especially true for biologic medicines, which are typically complex molecules produced by living cells, and are increasingly the backbone of modern therapy.

We've set out in recent months to advance new policies that are aimed at promoting more competition when it comes to biosimilar products.

In 2019, we plan to take some additional new steps to promote these goals, and I want to outline some of those actions today.

Until recently, biologics lacked effective competition because there was no abbreviated pathway for bringing generic versions of biologics to market under the Public Health Service Act (PHSA), similar to the pathway we have for small molecule drugs under created under the 1984 Hatch Waxman amendments to the Federal Food, Drug, and Cosmetics Act (FD&C Act).

The new approval pathway for biosimilars, enacted in 2010, allows an applicant to rely on the FDA's finding of safety and effectiveness for a biological reference product to support approval of a biosimilar and, therefore, develop the product at a potentially lower cost than the original reference product, provided the sponsor can demonstrate that the product meets the statutory standards for biosimilar approval.

The Biosimilars Action Plan we released last July advances our ongoing implementation of the Biologics Price Competition and Innovation Act (BPCIA). The plan improves the efficiency of the biosimilar and interchangeable product development and approval process. It increases scientific and regulatory clarity for the biosimilar development community. It provides for more communication and outreach plans for educating patients, clinicians and payors about biosimilars' safety and effectiveness. And it takes a number of steps to help address branded companies' gaming of FDA requirements.

The market for biosimilars continues to improve and I'm optimistic that it'll continue to evolve toward a viable and robust pathway. But we also face headwinds, and I know the pace of progress has disappointed some. I'm not discouraged. I believe it will take time for this market to mature. But that doesn't mean we don't face critical challenges. And it doesn't mean that we have the right policy framework to realize these opportunities. There's more that we need to be doing — all of us.

The good news is that in the past year, we approved a record number of biosimilar products — seven in all, for a total of fifteen approved products. And the FDA currently has more than 60 biosimilar development programs ongoing. We held a Part 15 hearing in September, to hear from the community how we can continue to advance meaningful development of the biosimilars market.

I know a lot of these drugs never launched owing to patent issues. Like the early days of Hatch Waxman, there are legal issues that are being worked out related to the patents governing these products, and the kinds of deals that companies strike with each other. This is a dynamic market, and we'll continue to address potential barriers to competition as they emerge, including in partnership with colleagues at the Federal Trade Commission.

Today, we're taking additional actions to advance this framework. Among them, we're issuing four new guidance documents today.

The first two guidance documents provide greater clarity on scientific and regulatory considerations for the development of biosimilar and interchangeable products. We intend to update these new guidance documents regularly, to address development issues as they evolve.

I want to draw particular attention to one critical issue we addressed in the draft Q&A guidance we're releasing today. It relates to companies using — and sometimes abusing — limited distribution systems, sometimes in connection with Risk Evaluation and Mitigation Strategy (REMS) programs, as a way to delay or derail access to reference product samples that biosimilar sponsors need for testing to support their applications for a biosimilar product. While the limited distribution programs can have a role in promoting patient safety, too many branded products are still misusing these programs as rhetorical smokescreens to hide anti-competitive behavior.

We're not going to be partners to these deceptions.

I've called out these practices when it comes to small molecule drugs. And we've posted a web

site that identifies cases where generic sponsors have had difficulty getting access to the doses of a reference drug that they need in order to conduct the studies to seek a generic approval.

We're now going to be focusing equal attention to these same potentially anti-competitive practices when it comes to biosimilar drugs.

To start, today, we're issuing notice of how the FDA will — upon request — review study protocols submitted by biosimilar applicants to assess whether their protocols contain comparable safety protections to those in the REMS for the reference product they're trying to reference. If requested, the FDA will issue a letter to the reference product holder informing them that comparable protections exist, and that the FDA won't consider it to be a violation of the branded drug company's REMS to provide the biosimilar sponsor with a sufficient quantity of the reference product to perform testing necessary to support its biosimilar application.

This is just a start.

We're going to be monitoring these markets. And we'll be taking additional actions. We're actively evaluating how we can make it easier for biosimilar manufacturers to use reference products from outside the U.S., where prices may be cheaper and reference products more accessible.

We're also releasing today two critical guidance documents that describe how the agency plans to implement Congress' direction that we transition certain biological products currently approved as drugs under the FD&C Act to be licensed as biologics under the PHSA.

Transitioning these drugs to the PHSA will let them to be treated as biologics under that law. And that means opening them up to competition through the biosimilars pathway. This includes insulin, which has been historically regulated as a drug and not a biologic.

Starting in March 2020, the approved marketing applications for the small subset of "biological products" such as insulin and human growth hormone — which for complex historical reasons were previously generally approved as drugs under section 505 of the FD&C Act — will be deemed to be biologics licenses under section 351 of the PHSA. Sponsors have known about this transition for a decade. They've had time to prepare.

Today, we're laying out our policy on how these products will transition from the drug pathway to the biologics pathway, and in so doing, how we intend to use this new framework to promote competition. The two guidance documents we're releasing today, one final and one draft, describe how the FDA intends to accomplish the transition of these products under the "Deemed to be a License" provision of the BPCI Act. The final guidance deals with "Interpretation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009," finalizes the FDA's draft guidance from 2016.

We've shaped these policies to implement the intent of Congress, and to make sure a few things happen. First, that the anti-evergreening provisions under the biosimilars legislation — meant to prevent sponsors from being able to game the exclusivity provisions to forestall biosimilar entry —

will apply to these newly deemed products, including insulin.

And second, we wanted to make sure that as these drugs transition to the biologics pathway, they don't receive additional exclusivities that they aren't entitled to. They don't get to start benefiting from the 12 years of exclusivity that the law grants to newly licensed biologics, just because these drugs — some of which were approved decades ago — are being treated as biologics for the first time. Once their patents have lapsed, and certain previously awarded exclusivities like orphan drug protection, have run their course, these products can be open to brisk competition from biosimilars.

This transition of biological products currently regulated as drugs to being regulated as biologics will enable, for the first time, products that are biosimilar to, or interchangeable with, these products to come to market. This is a watershed moment for insulin products, which millions of American take each day to maintain stable blood glucose.

There are currently no approved insulin products that can be substituted at the pharmacy level. One reason is that it was hard to bring a substitutable generic insulin to the market under the conventional drug pathway. The biosimilar pathway should make this kind of competition more accessible. Once an interchangeable insulin product is approved and available on the market, it can then be substituted for the reference product at the pharmacy, potentially leading to increased access and significantly lower costs for patients.

The final guidance provides recommendations to sponsors of proposed biological products that are intended for submission in a New Drug Application (NDA) that may not receive final approval under the drug pathway of the FD&C Act by March 2020 to carefully consider how they can align their development plans to account for the transition provisions of the new biologics pathway. Biological products that have been approved under section 505 of the FD&C Act will be removed from the FDA's Orange Book on March 23, 2020, based on the agency's position that these products are no longer "listed drugs." That means that a follow-on applicant won't be able to rely upon these NDAs for approval. They have to go down the biosimilars path after the transition. Products approved in NDAs that are deemed to be Biologics License Applications (BLAs) will be included in the Purple Book, which lists biologics licensed by the FDA under the PHSA.

The final guidance also describes the FDA's plans for supplements to approved NDAs that are pending under the FD&C Act on March 23, 2020. We intend to administratively convert these pending NDA supplements to pending BLA supplements under the PHS Act. We're doing this to minimize possible disruption caused by the transition provisions of the BPCIA and provide clarity and certainty to application holders who seek to make changes to their products close to the transition date.

We carefully considered all comments received on the prior draft guidance as we developed the final guidance and clarified certain aspects of the agency's interpretation of the statutory transition provision. These biological products that will be deemed to be licensed under the Public Health Service Act won't be eligible for a 12-year period of reference product exclusivity. We will

not confer exclusivity that sponsors never expected nor were intended to receive. There's nothing in the BPCIA to suggest that Congress intended for biological products approved under the FD&C Act to obtain a 12-year period of reference product exclusivity upon being "deemed to be licensed" under the PHSA. Some of these products were approved many years ago. Their exclusivities, and even their patents, have lapsed.

The FDA is working to ensure that there's a seamless transition of approved NDAs for biological products that will be deemed licensed BLAs, and that there are minimal impacts on manufacturers and patients. Patients on medications that will transition from being regulated under an approved NDA to a deemed BLA won't be affected by the transition.

We're at a crucial stage in the development of a competitive market for biological products and the FDA is committed to efforts that advance the science and policies to make the development of biosimilars and interchangeable products more efficient. These changes and opportunities are long overdue — especially when it comes to insulin.

Insulin is a hormone that regulates sugar metabolism. When the body doesn't make enough effective insulin, it can lead to diabetes — both the inherited Type 1, and Type 2, typically called adult onset. Diabetes affects nearly 30 million Americans. It can lead to serious and life-threatening complications, including heart disease, organ failure and blindness. It remains the seventh leading cause of death in the U.S.

A recent study suggested that accounting for all deaths attributable to diabetes could make it the third leading cause of death, since a diabetic killed by a heart attack may have heart disease listed on his death certificate even though the ultimate cause was poorly controlled diabetes. It also accounts for $330 billion in annual health care spending.

While many patients with Type 2 diabetes can control their diabetes through diet, exercise and oral medications, like metformin, more than seven million diabetics require daily insulin injections to maintain glycemic control and reduce the risk of complications.

Access to affordable insulin is literally a matter of life and death for these Americans. This is a challenge, even though insulin was discovered nearly a century ago by a Canadian research team led by the orthopedic surgeon Frederick Banting in 1921. In 1923, Banting's team was awarded a U.S. patent which the team sold to the Board of Governors of the University of Toronto for a grand total of $3.00.

Today, insulin list prices regularly increase by double digits annually. In mid-November, the Congressional Research Service reported that the list price of one type of insulin had increased nearly 600 percent from 2001-2015, from $35 dollars a vial to $234. Another study from the Schaefer Center at USC found that "the average U.S. list price of [four insulin categories] increased by 15% to 17% per year from 2012 to 2016."

The new pathway we're laying out today should help usher in a new era of competition for these products that'll lead to lower prices and better access. Change won't happen overnight. But we've

crafted this policy to meet the needs of patients. It's an opportunity that can't come soon enough for the thousands of Americans who struggle to pay for insulin.

The science has advanced to meet these policy opportunities. More companies are poised to enter this space and stimulate competition. Insulin production methods have improved significantly since Banting's time. Insulin used to be extracted with great difficulty and expense from cow and pig pancreas cells. Beginning in 1982, recombinant DNA technologies allowed for efficient production of humanized insulin from microorganisms. Now that technology is ubiquitous.

But despite these advances, limited competition in the insulin market has helped keep prices artificially high. Today, according to the Congressional Research Service, three firms control 90 percent of the global insulin market, and produce all the insulin used in the U.S.

FDA research shows that drug prices are directly related to the number of generic manufacturers in the market. The first generic competitor to market offers only a small discount to the branded product. But once three or more generic competitors enter the market, discounts can rise to 80 percent or more of the branded price.

Ironically, drug makers often keep a relatively small fraction of the list price increases they take. Patients who are uninsured or under-insured may be out of pocket for these price hikes. But we can't even argue that the price increases are plowed back into more research. They're not.

Instead, drug manufacturers use rebates generated by the gap between their rising list and net prices to pay for preferred status on pharmacy benefits managers (PBM) formularies. Monopoly profits benefit every member of the drug supply chain, except the patients who most need access to affordable products. This includes diabetic patients in high deductible health plans who can find themselves paying list prices for these drugs that no one else pays.

As a result, we've heard frequent reports of patients rationing insulin, and in some cases dying because they can't afford the injections they need to survive. These tragic stories aren't isolated occurrences. And they're not acceptable for a drug that's nearly a century old.

The transition of biologics currently regulated under the FD&C Act to the PHSA will open the pathway to market for new insulin products that are biosimilar to, or interchangeable with, the legacy reference products.

Given our long experience regulating insulin products, and high interest among sponsors who are proposing to develop interchangeable insulins, we're confident that interchangeable insulins — insulins that will be available for automatic substitution at the pharmacy level — will be attainable after the transition to deemed BLAs in March 2020.

I know that won't be soon enough for patients that are suffering today, and don't have secure access to needed medicines. We're taking other steps to bring more competition to the market. And we're encouraging sponsors that are developing new products to fashion these applications and development programs with an eye toward this new framework.

The drug industry argues that the high prices on truly innovative and transformative medicines help sustain the investment in these endeavors and support future cures. That's only part of the story. Investment decisions are based on the total amount of cash flow return that an endeavor can generate. But equally if not more important are the profitability of these enterprises. And profitability — and the high margins enjoyed by the life science industry — isn't just a function of the prices being charged. It's also affected by the cost of these endeavors. If we can bring more certainty to these endeavors, and define development pathways that are more efficient, we can maintain the profitability — and in turn the incentives to invest — without relying on rising prices.

This is how efficient regulation — and clear guidance that helps reduce costs by reducing uncertainty — can allow research and development to remain constant even while prices of innovative products fall. That's where we should be focused. When stakeholders are focusing inordinate time and energy protecting monopoly rents on legacy products through restrictive rebating and contracting practices, they lose focus on truly innovative development programs. Everyone loses in the long run. Especially patients. Through this myopic lens, a stagnating present seems more attractive than an innovative, but challenging future.

Responsible risk taking is at the heart of the innovative process. It's a passion for innovation that still thrives in many companies, who know that the most serious threat to the industry's long-term health is the public's sense that the social contract between the quests of innovators and the needs of patients has been breached by greed or apathy.

I'm optimistic that the abiding faith of those who make their living probing science and developing new medicines will remain innovation, access and the advance of public health. I'm optimistic about the many promising technologies — including regenerative cell and gene-based therapeutics — that have the potential to transform once intractable ailments, including diabetes. But these aspirations need to be married to smart policy that puts appropriate guardrails on these endeavors to steer them down the most productive lanes. I'm committed to those policies.

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