RECOMMENDATION 6: ADVANCE DRUG COMPETITION

Key takeaways:

- FDA has taken significant steps to advance drug competition under action plans that launched under the first Trump Administration and continued under President Joseph Biden.
- FDA should prioritize continued efforts under these plans and update them to account for changes under the IRA.
- FDA should further streamline the pathway for interchangeable biological products.

Although FDA does not regulate the price of drugs, its policies can nonetheless have a significant impact on prices—both by setting regulatory requirements that affect the cost of developing and marketing drugs, such as those discussed in other sections of this paper, and by encouraging competition between drug products. Such competition can take the form of follow-on products that are identical or similar enough to the original version that they can be used as substitutes and compete directly on price (e.g., generic drugs and biosimilars), or in the form of products in the same therapeutic class that may not only potentially compete on price but also provide important clinical differentiation for patients who may respond better to one drug than another.[211]

FDA has taken significant steps to advance drug competition under the Drug Competition Action Plan (DCAP) and Biosimilars Action Plan (BAP), which were launched under the first Trump Administration and continued under President Biden.[212,213] Going forward, the agency should (1) continue and expand upon the successes of DCAP and BAP, including by addressing changes to the competitive landscape introduced under the IRA and (2) further modernize the framework for developing versions of biological products that can be substituted at the pharmacy.

Recommendation 6.1: Continue the Drug Competition Action Plan and Biosimilars Action Plan, and update them to account for changes under the IRA

Under the DCAP and BAP, FDA has been advancing policies and programmatic reforms to encourage increased competition within the frameworks established by Congress. These frameworks, established under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act)[214] and the Biologics Price Competition and Innovation Act of 2009 (BPCIA),[215] balance the goals of incentivizing innovation and facilitating competition by combining periods of statutory exclusivity for novel products with efficient processes for identical or highly similar follow-on products (called generics for drugs and biosimilars for biologics) to obtain approval and resolve patent disputes.

Under these frameworks, a generic or biosimilar developer can avoid the time and expense of duplicating the studies that supported FDA's findings of safety and effectiveness for the brand-name product, and instead focus on demonstrating that its product is the same as, or similar enough to, the brand-name version and can therefore rely on FDA's earlier findings that the product is safe and effective.[216,217] The relevant showings are:

- A generic drug must show that it is "bioequivalent" to the brand-name version, meaning that it works in the same way and provides the same clinical benefit.[216,218]
- A biosimilar must show that it is highly similar to the brand-name biologic with no clinically meaningful differences.[219]

The different standards reflect that biological products are typically complex molecules for which inherent variation can be a natural part of the manufacturing process, as long as it is not clinically meaningful.[220]

This system has been remarkably successful in expanding patient access to safe and effective medicines at lower cost. Today, generics and biosimilars account for more than 90% of prescriptions dispensed in the United States, but only 13% of prescription drug spending.[221] In 2023, the average out-of-pocket cost to fill a generic prescription was $7.05, nearly four times less than the cost of a branded drug,[222] and savings increase further when there are multiple generic versions of the same product.[223]

As for biosimilars, while they are a newer product category that has not yet reached the same level of penetration—the first biosimilar license in the United States was not granted until 2015—they still have a significant impact on patient access. Among molecules subject to biosimilar competition, biosimilars accounted for 24% of the market in 2021, and the costs for those molecules (including both originator and biosimilar products) were down between 18% and 50% per unit.[222,224]

DCAP and BAP encompass a variety of policy initiatives and programmatic reforms intended to increase the number of approved generics and biosimilars and facilitate faster market entry for these follow-on products. The actions advanced under these initiatives have included:

- Issuing guidance documents to provide increased regulatory clarity for generic and biosimilar product developers, including through hundreds of product-specific guidance documents to help developers identify appropriate methodologies and generate the evidence to support their applications[225,226]

- Improving FDA's application review processes to reduce both the time that applications spend in agency review and the number of times an application must be returned to a sponsor to address deficiencies[227]
- Publicizing a list of drugs that are off-patent and off-exclusivity without any approved generics to encourage generic development for those products[228]
- Expediting review of generic applications for drugs with limited competition (e.g., three or fewer approved drug products)[228,229]
- Educating clinicians, patients and payors—who may have questions about the biosimilar product category given how recently it first became available in the United States—to reduce underutilization due to limited awareness or misconceptions[213]

FDA should continue to prioritize these efforts to help generic and biosimilar developers bring safe and effective products to the market as efficiently as possible. This means, for example, ensuring that the agency continues to make available the resources necessary to publish new product-specific guidance documents and update other public resources, such as the list of off-patent, off-exclusivity drugs. These are not static resources; the universe of products eligible for generic or biosimilar competition continually evolves as patents and exclusivities expire. Likewise, market dynamics are not static, and new barriers to competition can emerge over time and require updated policy responses. FDA leadership should ensure that the agency is equipped to carry this important work forward.

In addition to continuing with existing efforts under DCAP and BAP, FDA should update these plans to include specific actions to address the impacts of the IRA on competition. Although CMS, not FDA, is responsible for setting the "maximum fair prices" that Medicare will pay for prescription drugs and biologics under the IRA,[45] that price-setting process will affect how manufacturers approach competition under the Hatch-Waxman Act and the BPCIA. FDA's work under DCAP and BAP should include monitoring how the IRA is affecting the programs it administers and taking appropriate responsive action.

The potential impacts are significant. For one thing, the IRA could reduce generic competition by reducing incentives for generic and biosimilar manufacturers to enter the market. The Hatch-Waxman Act creates a powerful incentive for generic manufacturers to enter the market as soon as legally permitted by awarding the first generic drug manufacturer that successfully challenges the originator's patent 180 days of exclusivity as the sole generic.[230] The BPCIA likewise creates incentives for the first biosimilar that is interchangeable with its reference product.[217] However, the lower maximum prices for branded drugs and biologics under the IRA could reduce the prices that generic and biosimilar manufacturers can charge, reducing the value of their statutory exclusivities and lowering incentives for generic and biosimilar entry.[46]

Theoretically, the IRA also creates a counter-incentive by excluding products with generic or biosimilar competition from the CMS price-setting process, meaning that if generic or biosimilar entry occurs early enough, a product may never be subject to a maximum fair price. This structure creates a potentially significant incentive for brand manufacturers to encourage competition, but CMS has diminished the value of that incentive through guidance. Specifically, CMS has taken the position that a generic or biosimilar "is marketed" for purposes of the IRA only if CMS determines, based on the "totality of the circumstances," that the competitor is engaged in "bona fide marketing."[231] This vague standard, which does not appear in statute, could limit the IRA's incentive for competition by creating substantial uncertainty as to when competition will be considered sufficient to exclude a product from being subject to a maximum fair price.

In addition, the IRA could limit the potential for competition between branded products within the same therapeutic class—both on price and through clinical differentiation. Although the maximum fair price applies only to the drug or biologic for which it is set, it could apply market pressure to other drugs in the same therapeutic class. For example, if a developer is considering investing in a branded competitor to a product that has already been marketed for several years, it may face a limited period of time—as little as nine years from the time the *first* product in the class began marketing[45]—before the market effects of IRA price setting begin limiting its own return on investment. The impact on follow-on branded products could have significant public health implications because of the important role these products play in the therapeutic ecosystem, such as by providing improved benefit-risk profiles and additional options for patients, in addition to potentially driving competitive pricing.[232]

Given these potential impacts, FDA should update DCAP and BAP to include efforts such as (1) closely monitoring drug and biologic development activity for signals of how firms may be responding to changes in the incentive structure, (2) coordinating with CMS so that IRA implementation is well-informed about potential impacts to programs that FDA administers and agency leaders can work through competing considerations, and (3) developing FDA policies to help restore incentives that might be unintentionally diminished under the IRA, such as additional policies for expediting review in appropriate cases.

Recommendation 6.2: Further streamline the pathway for interchangeable biological products

FDA should also move beyond DCAP and BAP to facilitate increased competition in the biologics market. One significant opportunity is reforming the process for establishing that a follow-on biological product is "interchangeable" with its brand-name counterpart—meaning that a pharmacist can substitute it for the corresponding brand version unless the prescription specifies otherwise. The process as it currently stands poses unnecessary regulatory barriers to the utilization

of biosimilars, and while FDA has adopted several meaningful reforms, much more can be done.

There is a pressing need for reform. The market for biologics has been growing considerably faster than the market for small-molecule drugs and now comprises nearly half of all pharmaceutical spending.[224] However, even while the overall biologics market grows, the rate of biosimilar competition is far lower than it could be. Although the rate is increasing, it has been doing so more slowly than many anticipated, and there is still no biosimilar under development for 86% of eligible brand-name biologics.[221]

The current framework for establishing interchangeability has been one of the significant barriers to greater utilization. Whereas all generic drugs that meet the statutory standard of bioequivalence can be substituted at the pharmacy,[216,218] unlocking substitutability for a biologic requires additional work. Unlike a generic drug, a follow-on biologic that is licensed as a "biosimilar" is not pharmacy substitutable and can be dispensed only if it was affirmatively allowed by the prescribing physician. To be substitutable akin to a generic, the product must make the additional, heightened showing that it is "interchangeable" with the brand-name version—a statutory requirement under which it must demonstrate that it can be expected to produce the same clinical result as the brand-name version in "any given patient," and that switching or alternating between the two versions of the product does not create additional risks for patients.[219] Historically, FDA has required developers making this showing to conduct comparative clinical studies to assess the risk of switching or alternating between the biosimilar and brand-name versions of a product (e.g., "switching studies").[233]

This two-tiered approach was designed to protect patients against potential adverse effects of switching between versions of a product, such as harmful immune responses. However, it has also limited patient utilization by requiring a version-specific prescription unless the product can meet the heightened bar of interchangeability. It also differs from frameworks in other countries; the European Union, for example, approves a single type of biosimilar without restrictions on interchangeability.[234,235]

In recent years, FDA has begun rethinking its implementation of the interchangeability requirement. As the agency has gained more experience with biosimilars, and has had the benefit of observing a different regulatory approach in Europe, it has taken several actions to simplify the process for establishing interchangeability while maintaining appropriate safeguards for patients:

- *Insulin guidance:* In 2019, FDA issued a policy stating that, given the substantial history of patients safely switching between insulin products, comparative analyses like switching studies would not be necessary for biosimilar insulin to be licensed as interchangeable.[236] This policy change paved the way for FDA to begin licensing interchangeable insulin biosimilars, including the first-ever interchangeable biologic in 2021.[237]
- *"Intent to revise" guidance:* In 2024, FDA issued a "draft update" to its guidance on demonstrating interchangeability in which it stated that it intended to revise the guidance to simplify the interchangeability process for all biosimilar products. The document explained that, based on FDA's further experience with biosimilars and advancements in analytical technologies, comparative analyses like switching studies would no longer be necessary for any biosimilar to establish interchangeability. However, an applicant who chooses to forgo comparative analyses would still have to submit an "assessment" describing how other data in the application satisfy the statutory interchangeability standard.[238,239]

The 2024 "intent to revise" guidance represents a marked shift in the agency's approach to interchangeability, which could facilitate a substantial increase in the amount of interchangeable competition. But the draft is short on practical details. Going forward, FDA should prioritize issuing the actual revised guidance and filling the relevant gaps, including with details such as what data or other information can satisfy the interchangeability standard without comparative analyses like switching studies; under what circumstances the agency intends to require comparative analyses; and how the agency intends to adjudicate disputes about whether comparative analyses are needed in a given case.

FDA should also continue to advocate for a legislative update to the interchangeability requirement. In past years, the agency has proposed legislation to eliminate the statutory distinction between biosimilar and interchangeable products altogether, and to deem all approved biosimilars as interchangeable. Legislation along these lines would further simplify the path to pharmacy substitution beyond what FDA can do under current law, but it also carries risks of unintended consequences and, to the extent that legislation moves forward, FDA should work with Congress to address them. For example:

- If the statute is updated to deem all biosimilars interchangeable, it should be clear that FDA retains the ability to require comparative analyses like switching studies if it finds them necessary in individual cases. Otherwise, the legislation could unintentionally reduce competition in some cases by putting the agency in the position of potentially having to deny a biosimilar application because it could not resolve whether the product can be switched with the brand version without patient risk.
- For similar reasons, any legislation should also clarify that FDA retains the ability to approve biosimilars as non-interchangeable if concerns remain regarding the risk of switching. This could be accomplished by clarifying that FDA may license a biosimilar with restrictions on its distribution—which could be implemented as part of a Risk Evaluation and Mitigation Strategy (REMS)[92]—to preclude pharmacy substitution. Such a provision would avoid a situation in which a biosimilar that is found to present a risk to patients when switching, but that otherwise satisfies the standard for biosimilars, might be denied licensure as a biosimilar to avoid this risk.