Center on
Health Policy
at BROOKINGS

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Dr. Martin A. Makary
Commissioner
Division of Dockets Management
U.S. Food and Drug Administration (FDA)
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 4) (Docket No. FDA-2011-D-0611)

Dear Commissioner Makary,

I appreciate the opportunity to comment on FDA's Draft Guidance, New and Revised Draft Q&As on Biosimilar Development and the Biologics Price Competition and Innovation Act of 2009 (BPCI) Act (Revision 4). The updates in Revision 4 reflect the Agency's continued effort to align regulatory requirements with advancements in the analytical tools available to drugmakers, with the goal of streamlining biosimilar development.

My comments on this draft guidance draw on over a decade of work as a healthcare economist studying how regulatory policy shapes drug development, competition, and patient access.[1]

I generally support the approach taken in Revision 4, particularly the revisions to Q&A I.8 and I.19, which clarify the use of non-U.S.-licensed comparator products. By allowing sponsors to meet FDA's requirements through more efficient means without lowering evidentiary standards, these updates should help reduce development costs and shorten timelines [1]. I commend the Agency for these improvements to the biosimilar approval pathway.

In this letter, I explain why these proposals are likely to lower costs and encourage development. I recommend that the final guidance strengthen its language around the use of well-characterized non-U.S. comparators as a valid scientific approach and also in granting chemistry, manufacturing, and controls (CMC) waivers for investigational new drug applications (INDs) attached to non-U.S. comparators. I also suggest that the Agency review the reserve sample requirements laid out in Q&A I.10 to ensure that the associated costs and benefits are appropriately balanced.

Beyond the guidance itself, I address broad issues that are outside FDA's direct authority but have a profound effect on biosimilar markets. The regulatory changes advanced here are designed to lower the cost and reduce the complexity of biosimilar development, with the aim of spurring competition, lowering prices, and expanding patient access. But the positive impacts of these regulatory changes may not achieve their full potential due to the commercial realities biosimilars face once on the market.

[1] The views expressed in this letter are my own and do not reflect the views of the Brookings Institution or anyone affiliated with the Brookings Institution other than myself.

The current insurance and pharmacy benefit manager (PBM) system often works against biosimilars, favoring products with high-list prices that generate larger rebates [2, 3]. Developers are well aware of these dynamics – even if regulatory costs were reduced to zero, the financial incentive to seek approval often remains weak when the path to formulary placement and market share is so uncertain [4]. These commercial barriers are outside FDA's authority, yet they are central to whether regulatory streamlining actually translates into more affordable options for patients. Meaningful gains in access will therefore require progress on two fronts: continued FDA efforts to make the approval process as efficient as possible, and reforms to the commercial environment that give biosimilar manufacturers a viable route to market success after launch.

Lowering development costs associated with the use of non-U.S.-licensed comparators

The revised Q&A I.8 describes how a sponsor may use comparative clinical data from studies based on a non-U.S.-licensed comparator product to support its proposed biosimilar product. This policy creates an avenue for reducing biosimilar research and development expenses; when an adequate scientific justification is provided, manufacturers can forgo redundant three-way pharmacokinetic bridging studies. The Agency has itself noted that eliminating such pharmacokinetic bridging studies can cut development costs by roughly $20 million, while the shift away from mandatory comparative efficacy studies can save an additional $24 million and one to three years of development time [5]. If these savings are realized, they would represent a reduction in the investment required to bring a biosimilar to market [1].

The revised Q&A I.19 complements this approach by clarifying that a single IND application can cover a development program involving a non-U.S.-licensed comparator and that, with appropriate justification, CMC waivers can be granted for that IND. This is a sensible policy. In many cases, a non-U.S.-licensed comparator is the same originator biologic manufactured under comparable quality standards, often in the same facility, and licensed by an ICH-compliant regulatory authority [6, 7]. FDA's willingness to consider waiving certain CMC requirements under 21 CFR 312.10 should help reduce administrative burdens without undermining data quality.

Together, these two policies, streamlining the use of non-U.S.-licensed comparators and granting CMC waivers for the associated INDs, can lower development costs and ease the review process. To maximize those gains, I encourage the Agency to explicitly endorse well-characterized non-U.S.-licensed comparator data as a standard and scientifically valid approach, and to reiterate its willingness to grant CMC waivers for INDs that rely on comparators manufactured under comparable quality standards and licensed by a trusted regulatory authority. Greater clarity on these points will give sponsors more certainty that their development programs will meet FDA's expectations.

Calibrating reserve sample rules to real-world testing frequency

The revised Q&A I.10 recommends retaining at least 200 mg of the reference and proposed products across 10 dosage units for five years. I do not question the scientific prudence of retaining reserve samples. From a cost-benefit perspective, however, the logistics of procuring, storing, and managing these lots, especially when the comparator is a non-U.S.-licensed product that must be imported and tracked separately, can add expense and operational complexity [8]. While this requirement is only one

component of total development costs, even small cumulative burdens can affect investment decisions for products with narrow expected returns [7].

I recommend that FDA periodically review the costs and benefits of this requirement, calibrating the amount of reserve sample needed based on the actual frequency and nature of post-approval investigations. If real-world experience shows that such testing is rare, or that smaller sample volumes would suffice for the analytical techniques in use, a flexible standard allowing sponsors to justify a reduced retention volume could further lower barriers without compromising the Agency's standards.

Commercial dynamics, not regulatory costs, often deter biosimilar entry

More than 100 biologics are expected to lose patent protection over the next decade but have no biosimilars in development, a gap that could represent an estimated $189 billion in lost savings [9]. Improvements in FDA regulatory policy may help spur development of some of these biosimilars, but other challenges remain. For example, many of these biologics treat rare diseases or hold narrow indications, serving patient populations too small to support multiple competitors, regardless of how efficient the regulatory pathway becomes [4, 9].

Even in larger markets, biosimilars face formidable commercial obstacles. They often struggle to secure formulary placement and gain market share after approval – post-approval commercial viability remains a central consideration for makers of biosimilars [4]. The economic incentive to pursue biosimilar development depends not only on the cost of obtaining FDA approval, but also on the expected financial return once a product reaches the market. In the current U.S. healthcare system, access is heavily shaped by rebates and formulary management practices that can decouple a product's net price from its likelihood of being covered [10]. Vertically-integrated PBMs frequently favor high-list-price products that generate large rebates and, increasingly, prefer their own private-label biosimilars over independent biosimilars, even when the independent products have lower net costs [4, 11]. In this environment, a lower list price can become a commercial liability because it generates a smaller rebate pool, a dynamic that deters prospective biosimilar developers.

These market access issues fall outside FDA's jurisdiction, but they are essential to understanding how to motivate biosimilar development. Addressing them will require action by other agencies, including the Centers for Medicare and Medicaid Services (CMS) and the Federal Trade Commission (FTC). FDA can contribute by continuing to refine its own policies to complement scientific advances and by making clear, through interagency discussions, that commercial barriers are limiting the practical impact that even the most efficient regulatory pathway can have on the number of approved biosimilars. If biosimilars cannot reliably secure formulary placement and market share after approval, lower development costs alone will not translate into a larger pipeline.

Clarifying the guidance while acknowledging the limits of FDA's reach

Revision 4 of the Draft Q&As on Biosimilar Development and the BPCI Act moves the regulatory framework in a positive direction, especially in its treatment of non-U.S. comparator data and IND requirements. The recommendations below aim to reinforce that direction and add clarity where uncertainty remains.

First, for Q&A I.8, the final guidance could more explicitly endorse the use of well-characterized non-U.S.-licensed comparator data in regulatory submissions, treating it as a standard and scientifically valid approach. Clearer language would reduce regulatory uncertainty and could expand the pool of firms willing and able to pursue biosimilar development.

Second, for Q&A I.19, FDA could reiterate its willingness to grant CMC waivers for INDs, citing non-U.S. comparators manufactured under comparable quality standards and licensed by a trusted regulatory authority. Such waivers would reduce documentation requirements, helping sponsors avoid delays and move forward with greater confidence in their development timelines.

Third, for Q&A I.10, the Agency could periodically review the reserve sample requirements to ensure they reflect current analytical capabilities and actual post-approval testing experience, allowing flexibility where scientifically justified.

Finally, it is important to recognize that even a perfectly streamlined regulatory pathway cannot, on its own, deliver robust biosimilar price competition. Firms invest based on expected financial returns, which depend heavily on the ability to secure formulary placement and gain market share [8, 10]. As described above, the current commercial environment, characterized by rebate-driven formulary management and vertical integration, often works against lower-cost independent biosimilars. These commercial realities lie beyond FDA's regulatory reach, yet they largely determine whether lower development costs actually lead to more approved biosimilars, lower prices, and broader patient access. Addressing these issues will require action by other agencies, including CMS and FTC, as well as continued interagency collaboration to improve the market landscape for biosimilars. For its part, FDA can ensure that its own policies continue to evolve alongside scientific advances, and it should clearly communicate how external barriers dull the impact of its regulatory improvements.

I appreciate FDA's continued efforts to align policy with scientific progress and thank the Agency for the opportunity to provide these comments.

Respectfully submitted,

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