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# Development of Biosimilar and Interchangeable Biological Products During the COVID-19 Pandemic: What the ANDA Guidance Left Unsaid

There has been much discussion about FDA's recently-issued guidance regarding the development and review of abbreviated new drug applications ("ANDAs") during the COVID-19 pandemic. The guidance, "Development of Abbreviated New Drug Applications During the COVID-19 Pandemic—Questions and Answers" ("*COVID Q&A Guidance*"),[1] also leaves much unsaid. Notably, the guidance stops short of extending the Agency's thinking on the articulated scientific and regulatory principles from small molecule generics to follow-on biological products, *i.e.*, biosimilar and interchangeable biological products.[2] There may be good reason for this: the biosimilars pathway differs from the ANDA pathway in a number of important ways, and the treatment of the two product categories by FDA has justifiably been separate in most cases. As we explain below, however, the *COVID Q&A Guidance*'s "case-by-case" approach to 180-day exclusivity for generics should be flexible enough to apply to first interchangeable exclusivity for interchangeable biosimilar products, too.

Read on for our analysis and insights, and please stay tuned as we continue to watch for answers to lingering questions.

## WHAT DOES THE *COVID Q&A GUIDANCE* COVER?

The *COVID Q&A Guidance* covers a wide range of issues related to the development of generic drugs during the COVID-19 pandemic, ranging from how to handle expiry of test batches and reference product batches when studies are interrupted or delayed[3] to whether the Agency will accept bioequivalence studies based on non-U.S.-approved products during the pandemic (per FDA policy, the answer is: no).[4] It also answers questions about the submission and assessment of ANDAs for products that may be used to help address the pandemic or that may otherwise be

affected by the pandemic.[5] For example, the guidance explains that if an ANDA lists a manufacturing site that cannot be inspected due to COVID-19-related travel restrictions, the application will not automatically receive a complete response letter.[6] Instead, FDA expects to base its decision on the totality of available information, including information obtained through alternative inspection tools, as described in additional FDA guidance.[7] These alternative inspection tools include requesting records in advance, or in lieu, of inspection;[8] relying on recognized, non-U.S. agency inspections; and leveraging the newly-announced "remote interactive evaluations" of manufacturing facilities to inform approval decision-making.[9]

The last question and answer in the *COVID Q&A Guidance* discusses the impact of COVID-19-related inspection delays on exclusivity for ANDAs. This Q&A explains that, if FDA cannot take action on a pending, first-to-file ANDA due to COVID-19-related travel restrictions and the 30-month deadline for the ANDA applicant to obtain tentative or final approval passes, FDA will determine, on a case-by-case basis, whether a "first applicant" (*i.e.*, the holder of a first-to-file ANDA including a Paragraph IV patent certification) is entitled to 180-day exclusivity or whether that exclusivity has been forfeited.[10]

The *COVID Q&A Guidance* stops short of saying whether, or how, loss of exclusivity due to inspection-related delays might be evaluated (for example, whether such delays might be considered an exclusivity-preserving "change in or a review of the requirements for approval … imposed after the date on which [an] application is filed"[11]), explaining instead that FDA will take all of the facts and circumstances into consideration in making exclusivity determinations, *i.e.*, a "case-by-case" analysis.[12] Similarly, the guidance does not address the question of how exclusivity might play out in conjunction with inspection-related delays when there are multiple "first applicants," not all of whom have applications that are forestalled due to FDA's inability to inspect.[13] Under normal circumstances, when multiple substantially complete ANDAs containing paragraph IV certifications are submitted on the same day, FDA considers all of the applicants to be "first applicants" with an opportunity to share in 180-day exclusivity.[14] Commercial marketing by any first applicant then triggers the 180-day exclusivity period for all.[15] In the midst of a public health emergency, however, it is unclear—and the *COVID Q&A Guidance* does not say—whether FDA might consider missing a user fee goal date for a second applicant under such circumstances. In fact, FDA's case-by-case analysis framework may be filled with landmines if the Agency ends up needing to navigate these complex equities.

FDA has acknowledged that "[t]he 180-day period of generic drug exclusivity provides a very strong financial incentive for an ANDA applicant to challenge a patent that it believes it does not infringe or that it believes is invalid or unenforceable,"[16] and FDA has given a great deal of focused attention to incentivizing generic competition in recent years, as outlined in the 2017 FDA Drug Competition Action Plan and Agency actions under that plan.[17] So it seems likely that FDA would go to great lengths to avoid a situation in which an ANDA applicant loses exclusivity to which it otherwise would be entitled because of the Agency's pandemic-related inability to conduct a pre-approval inspection. It also makes sense that FDA would not draw that bright line in guidance, falling back instead on the "case-by-case" analysis to preserve its flexibility in the event of extraordinary circumstances.

## WHAT ABOUT BIOLOGICS?

At the end of the day, the *COVID Q&A Guidance* may be more notable for what it did not say than for what it said. The guidance talks about developing generic drugs and submitting ANDAs, but it is silent regarding the development of biosimilar and interchangeable biological products and the submission of 351(k) BLAs. Stakeholders are left to wonder whether the principles outlined in the *COVID Q&A Guidance* can inform treatment of follow-on biologics.

As mentioned above, there are good reasons why biosimilars are treated separately in statute and FDA guidances. Among other things, section 351(k) of the Public Health Service Act ("PHS Act") contains its own abbreviated pathway for approval, its own requirements for submission and licensure of biosimilar or interchangeable products, its own

scientific considerations, and its own unique exclusivity provisions. Approval of generic drugs is predicated on a demonstration of bioequivalence (among other things),[18] while approval of biosimilar products is based on a demonstration that the biosimilar is "highly similar" to and has "no clinically meaningful differences" from the reference product (among other things).[19] Approval of an interchangeable biosimilar requires a further demonstration that the proposed product is biosimilar to the reference product, will produce the same clinical result in any given patient, and that there will not be any risk of diminished safety or efficacy from switching back and forth between the interchangeable product and the reference product.[20] Also unlike generics, which are required to have the "same labeling" as the reference product,[21] labeling for biosimilar and interchangeable products is not required to be the same as the labeling of the reference product.[22]

The list of differences is substantial. However, as with generics, FDA has been outspoken in recent years about the critical role of biosimilar and interchangeable products in improving patient access and striking the Biologics Price Competition and Innovation Act ("BPCI Act")[23] balance between innovation and competition.[24] This is clear from the 2018 Biosimilars Action Plan and subsequent FDA work under that plan.[25] Given the structural similarities between 180-day exclusivity for generic drugs and first interchangeable exclusivity for interchangeable biosimilars, then, it is notable that FDA did not publish concurrent guidance or make mention in the *COVID Q&A Guidance* of the applicability of the principles articulated in that guidance to 351(k) BLAs or applicable biologics exclusivity.[26]

In general, under section 351(k)(6) of the PHS Act, the sponsor of the first BLA to be approved as interchangeable with a biological reference product is eligible for a period of "first interchangeable exclusivity."[27] During that period of first interchangeable exclusivity, FDA is precluded from approving a "second or subsequent biological product" as interchangeable with that same reference product for any condition of use.[28] Eligibility for this exclusivity is based on approval of the first interchangeable biological product[29] (not filing, as with 180-day exclusivity for generics[30]), and the duration of the exclusivity period, which is calculated through a series of complex provisions enumerated in the PHS Act, can last anywhere from 12 months to several years.[31]

It would have been helpful for FDA to address the first interchangeable exclusivity considerations that may arise for interchangeable applicants who may have the approval of filed 351(k) BLAs affected by COVID-19 related inspection delays—even if only to say that the same "case-by case" approach described for 180-day exclusivity also would be appropriate for consideration of eligibility for first interchangeable exclusivity. Questions abound about what FDA's implementation of first interchangeable exclusivity will look like, but we know that the COVID-19 pandemic has had a significant impact on biosimilar review by FDA.[32] And, as the guidance calls to mind, one such unanswered question is this: if there are multiple filed interchangeable applications that reference the same reference product, will a second or subsequent application be able to leapfrog the first because the first is bogged down in a COVID-19-related inspection delay? Or will FDA consider those circumstances in the same type of "case-by-case" analysis laid out in the *COVID Q&A Guidance*? Given FDA's emphasis on the availability of the interchangeable pathway for insulin products[33] and the anticipation of additional interchangeable competition when blockbuster biological drugs come off patent in the next few years,[34] the impact of COVID-19-related inspection delays may need to be addressed sooner rather than later.

King & Spalding regularly counsels pharmaceutical and biologics manufacturers on drug development and exclusivity issues. Please let us know if you have any questions regarding drug development during the pandemic or 180-day or first interchangeable exclusivity.

## ABOUT KING & SPALDING

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[1] FDA, Guidance for Industry, *Development of Abbreviated New Drug Applications During the COVID-19 Pandemic—Questions and Answers* (Apr. 2021), https://www.fda.gov/media/147355/download) ("*COVID Q&A Guidance*").
[2] Unless otherwise specified, "biosimilars," as used throughout, includes "interchangeable" biosimilars. *See* Public Health Service ("PHS") Act § 351(k)(4), 42 U.S.C. § 262(k)(4).
[3] *COVID Q&A Guidance* at Q1/A1.
[4] *Id*. at Q5/A5.
[5] *Id*. at Q9/A9 - Q13/A13.
[6] *Id*. at Q13/A13.
[7] *Id*.; FDA, Guidance for Industry, *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers* (August 2020), updated on January 29, 2021 (https://www.fda.gov/media/141312/download).
[8] Federal Food, Drug & Cosmetic Act ("FD&C Act") § 704(a)(4), 21 U.S.C. § 374(a)(4).
[9] FDA, Guidance for Industry, *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency* (Apr. 2021), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remote-interactive-evaluations-drug-manufacturing-and-bioresearch-monitoring-facilities-during-covid.
[10] *COVID Q&A Guidance* at Q15/A15.
[11] FD&C Act § 505(j)(D)(i)(IV), 21 U.S.C. § 355(j)(D)(i)(IV).
[12] *COVID Q&A Guidance* at Q15/A15.
[13] *See* FDA, Guidance for Industry, *180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day* (July 2003), at 4, https://www.fda.gov/media/71304/download.
[14] *Id*.
[15] FD&C Act § 505(j)(B)(iv)(I), 21 U.S.C. § 355(j)(B)(iv)(I).
[16] *Id*. at 3.
[17] FDA, *FDA Drug Competition Action Plan* (updated Dec. 21, 2020), https://www.fda.gov/drugs/guidance-compliance-regulatory-information/fda-drug-competition-action-plan.
[18] FD&C Act § 505(j)(2)(A)(iv), 21 U.S.C. § 355(j)(2)(A)(v)); 21 C.F.R. §§ 314.101, 314.127; *see also* FDA Fact Sheet, What's Involved In Reviewing And Approving Generic Drug Applications? (undated), https://www.fda.gov/media/99163/download.
[19] PHS Act § 351(i)(2), 42 U.S.C. § 262(i)(2); FDA, Guidance for Industry, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (Apr. 2015), https://www.fda.gov/media/82647/download.
[20] PHS Act § 351(k)(4), 42 U.S.C. § 262(k)(4); FDA, Guidance for Industry, *Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry* (May 2019), https://www.fda.gov/media/124907/download.

[21] FD&C Act § 505(j)(2)(A)(v), 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94; *see also* FDA, Guidance for Industry, *Acceptability of Draft Labeling to Support ANDA Approval* (Oct. 2015), https://www.fda.gov/files/drugs/published/Acceptability-of-Draft-Labeling-to-Support-Abbreviated-New-Drug-Application-Approval--Guidance-for-Industry.pdf.
[22] FDA, Guidance for Industry, *Labeling for Biosimilar Products Guidance for Industry* (July 2018) ("*Biosimilar Labeling Guidance*"), https://www.fda.gov/media/96894/download); FDA*, Draft Guidance for Industry, Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (Nov. 2020), https://www.fda.gov/media/143847/download. FDA guidance recommends that biosimilar labeling "incorporate relevant data and information from the reference product labeling, with appropriate modifications." *Biosimilar Labeling Guidance* at 5.
[23] Biologics Price Competition and Innovation Act ("BPCI Act"), Pub. L. No. 111-148, §§ 7001 *et seq.*
[24] *E.g.*, FDA, *Biosimilars Action Plan: Balancing Innovation and Competition* (July 2018) at 1 (explaining FDA's role in striking "a balance between encouraging and rewarding innovation in drug development and facilitating robust and timely market competition"), https://www.fda.gov/media/114574/download.
[25] *Id*.
[26] Targeted FDA guidance often mentions other areas for which the principles articulated in such guidance may apply. For example, draft guidance entitled "Bridging for Drug-Device and Biologic-Device Combination Products" explains that some of the principles discussed in that guidance regarding "products submitted for approval under section 505(b) of the FD&C Act or licensure under section 351(a) of the PHS Act may also be applicable to products submitted for approval under section 505(j) of the FD&C Act or licensure under section 351(k) of the PHS Act." FDA, Draft Guidance for Industry, *Bridging for Drug-Device and Biologic-Device Combination Products* (Dec. 2019), at 1 n.4, https://www.fda.gov/media/133676/download.
[27] PHS Act § 351(k)(6), 42 U.S.C. § 262(k)(6).
[28] *Id*.
[29] *Id*.
[30] FDA, Guidance for Industry, *180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day* (July 2003), at 4, https://www.fda.gov/media/71304/download.
[31] PHS Act § 351(k)(6)(A)-(C), 42 U.S.C. § 262(k)(6)(A)-(C).
[32] *See* Derrick Gingery, "US FDA's On-Time Review Decision Rates Slip During The Pandemic, Especially For Biosimilars,*" Pink Sheet* (Mar. 16, 2021), https://pink.pharmaintelligence.informa.com/PS144003/US-FDAs-OnTime-Review-Decision-Rates-Slip-During-The-Pandemic-Especially-For-Biosimilars.
[33] *See, e.g.*, FDA Statement, *Insulin Gains New Pathway to Increased Competition* (Mar. 23, 2020), https://www.fda.gov/news-events/press-announcements/insulin-gains-new-pathway-increased-competition.
[34] *See generally*, Aurelio Arias, IQVIA, *Future Biosimilar Opportunities* (Dec. 23, 2019), https://www.iqvia.com/blogs/2019/12/future-biosimilar-opportunities.