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FDA Biologic Transition Plan Creates 'Dead Zone' For Applications, Sponsors Fear

by Sue Sutter

Industry objects to proposal that certain protein product applications pending as of March 23, 2020, will have to be resubmitted as BLAs – and to the idea that transitioned products will lose non-orphan exclusivity.

FDA's interpretation of the Biologics Price Competition and Innovation Act's "transition provisions" for certain protein products would create a "dead zone" or "blackout" period for new applications that could last several years, industry stakeholders say.

In comments responding to an FDA draft guidance on the BPCIA's "deemed to be a license" provisions, representatives from innovator, generic and biosimilar industries say the agency should allow pending NDAs and ANDAs for affected products to be reviewed and approved after March 23, 2020. That is the date when insulin, human growth hormone and other products that traditionally have been approved under the Food, Drug and Cosmetic (FD&C) Act will be deemed to be licensed as biological products under Section 351 of the Public Health Service (PHS) Act.

FDA's approach on exclusivity violates the Fifth Amendment's Takings Clause and free trade agreements, innovators said.

FDA proposes transition products that have not received final approval by March 23, 2020, would not be approved under the FD&C Act and must be resubmitted as BLAs. However, this approach would disrupt ongoing reviews, significantly impact development programs and dissuade companies from submitting applications under the FD&C Act long before the transition date,

industry representatives said.

"This proposal, if implemented, will have a devastating effect on current development programs for many important protein products, including insulin, thereby impairing competition for lower-cost biological medicines, increasing health care costs in the US and, most importantly, limiting patient access to affordable biological products," *Mylan NV*'s *comments* state.

FDA's proposal that transition products should lose marketing exclusivity also drew fire from some industry stakeholders. Innovator trade groups, individual insulin manufacturers and legal experts call for a more balanced approach, suggesting that unexpired marketing protections should carry over after products transition to BLA licenses or that such products should have the benefit of 12-year biologic exclusivity dating from original NDA approval.

These same commenters suggest FDA's proposed approach on exclusivity would represent a constitutional "taking" under the Fifth Amendment, thereby laying the groundwork for a legal challenge if the agency sticks to its original plan.

Protests Over Pending Applications

FDA's draft guidance, released in March, marked its first public explanation for how it planned to implement the BPCIA's transition provisions (Also see "*BLAs More Appealing As 'Transition' NDAs, ANDAs Set To Lose Exclusivity*" - Pink Sheet, 21 Mar, 2016.).

The agency said it would not approve any application under Sec. 505 for a biological product subject to the transition provisions that is pending or tentatively approved on March 23, 2020. Such applications may be withdrawn and resubmitted under 351(a), the traditional BLA pathway, or as a biosimilar under 351(k). In addition, FDA said it would remove affected biological products from the "Orange Book" on the transition date because these products would no longer be "listed drugs."

FDA acknowledged that its interpretation could have a significant impact on development programs for products in affected classes. It advised sponsors to evaluate whether planned submissions under Sec. 505 would allow adequate time for approval by the transition date and suggested they may want to consider submitting an application as a standalone or biosimilar BLA instead.

Most of the public comments disagreed with FDA's proposed handling of applications pending at the time of the transition date. This approach is contrary to the BPCIA's clear language, which allows sponsors to submit applications under Sec. 505 until the transition date, the comments said.

"FDA's proposed policy will force sponsors who are ready to submit applications for lower-cost

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biologics prior to March 23, 2020, to delay their submissions until after March 23, 2020, thereby significantly delaying the review, approval and availability of biological products that compete with expensive brand name biologics," the Generic Pharmaceutical Association (GPhA) and the Biosimilars Council's joint *comments* state.

> ***FDA's proposal "creates a regulatory 'dead zone' of a year or more between the time no rational sponsor would submit a 505(b)(2) application or ANDA … and the first date a biosimilar application could be submitted" – GPhA and the Biosimilars Council***

"For example, if a sponsor is ready to submit a 505(b)(2) application or ANDA for a transitional biologic in June 2019, FDA's proposed policy would provide a strong incentive for the sponsor to forgo any submission at that time because of the meaningful possibility that the application would not be approved prior to March 23, 2020," GPhA and the council said.

However, it also would be impossible for a sponsor to submit a biosimilar application prior to March 23, 2020, because, until that date, there would be no reference product licensed under Sec. 351 upon which an applicant could rely.

"FDA's proposed policy thus creates a regulatory 'dead zone' of a year or more between the time no rational sponsor would submit a 505(b)(2) application or ANDA (because of the likelihood it would not get approved in time) and the first date a biosimilar application could be submitted (i.e., March 23, 2020)," GPhA and the council said.

Similarly, the Pharmaceutical Research and Manufacturers of America's *comments* say FDA's proposal "would create a blackout period during which applicants would be unable to submit either NDAs or BLAs for their proposed medicines."

FDA's approach also would have a detrimental impact on supplemental NDAs pending at the transition date, commenters said. "We caution that FDA's proposal as it relates to sNDA submissions would slow down the approval of changes that may offer significant benefit to the public health (e.g., new indication, dosage form, or other change that enhances patient compliance or safety)," the Biotechnology Innovation Organization's *comments* state.

"While manufacturers that are considering an NDA for a new product may have more flexibility

to choose a BLA over an NDA from the start, a manufacturer pursuing a supplement is forced to work with the regulatory status of the currently approved product and thus would have to choose, essentially, between waiting until March 23, 2020, to submit its supplement or otherwise go ahead and submit as an sNDA only to then have to resubmit as an sBLA after March 23, 2020," BIO said.

Commenters suggest that NDAs and supplements pending at the transition date could be deemed BLAs during review, or they could retain their status until approval, at which time they would be licensed as BLAs.

The law firm Hyman, Phelps and McNamara suggests an approach that would recognize "a narrowly tailored cohort" of applications submitted by the transition date that would continue to be reviewed after the listed drugs they reference are deemed to have a license under Sec. 351. "This would serve to protect the substantial investment in a product's development in the face of longer than expected FDA reviews, requests for major amendments or multiple review cycles," the firm's *comments* state.

Wanted: Compromise On Exclusivity

In the draft guidance, FDA concluded that any remaining non-orphan exclusivities – five-year new chemical entity, three-year Hatch-Waxman, or pediatric – associated with an approved NDA subject to the transition provisions would cease to have any effect on March 23, 2020. Furthermore, nothing in the BPCIA suggests Congress intended to grant transition products a new 12-year period of exclusivity available to biologics licensed as standalone BLAs, the agency said.

FDA's hardline interpretation on exclusivity surprised some industry observers, who thought the agency would have tried to take more of a middle-of-the-road approach.

While the GPhA, Biosimilars Council and Mylan supported the agency's view, innovator groups said terminating existing exclusivity would be inconsistent with the BPCIA, harm innovation incentives and disrupt ongoing patent litigation.

"The draft guidance also raises constitutional issues concerning a taking of private property without just compensation in violation of the Fifth Amendment and threatens the nation's compliance with its free trade agreements," PhRMA said.

PhRMA and BIO suggest that any exclusivities in effect at the transition date should carry over until they would have expired under the FD&C Act.

"More broadly, until expiry of every Orange Book-listed patent, including any pediatric exclusivity extension, for a given listed drug, FDA should continue to treat the application for

that drug, as well as the follow-on applications that cite it, as Sec. 505 applications for exclusivity and patent purposes," PhRMA said, asserting that this approach would be less disruptive to sponsors of transition products engaged in Hatch-Waxman patent litigation.

Novo, Sanofi Eye Different Fixes

Insulin makers are expected to be among the biopharma companies most impacted by the transition provisions (Also see "*Insulin Exclusivity: How Big Will The Fight Be?*" - Pink Sheet, 21 Mar, 2016.).

Novo Nordisk AS' *Tresiba* (insulin degludec), approved in September, would lose several months of new chemical exclusivity under FDA's draft guidance. The company's *Xultophy*, a combination of Tresiba and the GLP-1 agonist *Victoza* (liraglutide), is under FDA review.

Novo said the exclusivity rights granted under a sponsor's chosen regulatory approval pathway should continue to apply after the transition date until they naturally expire. "Such an interpretation ... not only prevents conflict with the Takings Clause, but also avoids upsetting and creating greater uncertainty around any ongoing court litigation between sponsors," Novo Nordisk's *comments* state.

However, *Lantus* insulin maker *Sanofi* takes a different approach, saying that transition products should be eligible for the balance of 12-year reference product exclusivity for biologics dating back to their original NDA approval.

"This does not, as FDA asserts, provide windfall exclusivity to products approved 'decades ago,' nor does it stifle biosimilar or interchangeable competition 'until the year 2032,'" Sanofi's *comments* state, quoting from the draft guidance. "It is merely consistent treatment of all biological products, as Congress intended when it directed that all biological products should be unified under one regulatory scheme."

Sanofi said its investigational product combining Lantus (insulin glargine) and the GLP-1 agonist lixisenatide would be directly affected by the transition provisions, and it urged FDA to issue guidance that specifically addresses the impact on drug/biologic combinations (*see related story, (Also see "Insulin Makers To FDA: Clarify 'Transition' Impact On Drug/Biologic Combos*" - Pink Sheet, 23 May, 2016.)).