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Biosimilars In 2017: Crowded US FDA Review Queue, Key Legal Decisions

by Sue Sutter

At least five biosimilars could gain US licensure in the coming year on first-cycle review, including subsequent competitors to Remicade and Humira; however, patent litigation is expected to increase and will continue to slow the march of products from FDA approval to commercialization.

The US FDA's frenetic pace of regulatory activity in the Obama Administration's waning days may raise concerns that agency efforts to implement the biosimilar approval pathway could hit a lull in the coming months.

However, the 351(k) application workload currently at the agency and the pending reauthorization of the biosimilar user fee program, coupled with some key court decisions anticipated in biological patent disputes, suggests the next 11 months could be a key inflection point for biosimilars in the US.

The year could serve as the bridge between a still-nascent market with only two commercialized products, and a robust competitive enterprise with multiple biosimilars of the same product that results in the types of price reductions and access benefits the pathway's proponents have long envisioned.

FDA can expect to face a barrage of comments on its interchangeability guidance, but when it might be tasked with making its first designation remains a big unknown.

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There are at least five products with review timelines coming due in 2017, including some proposed first-in-class biosimilars. It's also possible that some previously rejected applications could be resurrected for review.

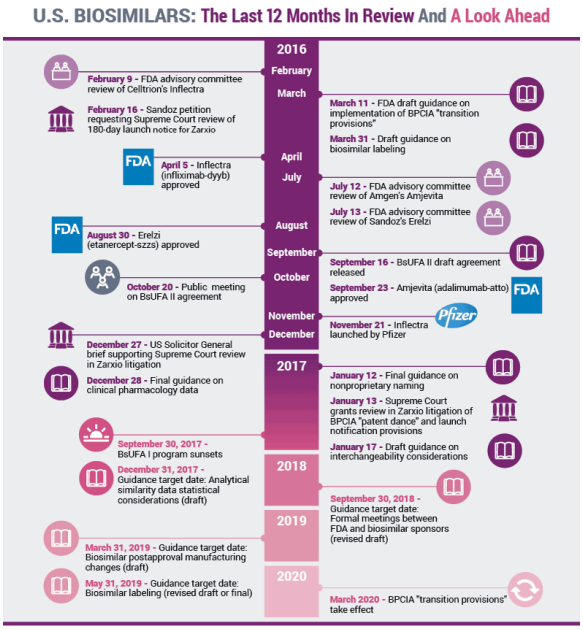
FDA can expect to face a barrage of comments on its recently released draft guidance on interchangeability considerations, but when it might be tasked with making its first designation remains a question.

One certainty ahead for 2017 is the need to renew the Biosimilar User Fee Act (BsUFA) program, the current iteration of which expires Sept. 30. The BsUFA II agreement negotiated in 2016 between FDA and industry would bring changes in the length of the review clock for 351(k) applications and a bolus of new funding for the agency's review and policymaking activities. However, the agreement must first pass muster with the new Congress and Trump Administration before it takes effect.

Despite all this anticipated activity on the regulatory front, federal court decisions may have a greater impact on whether 2017 closes with more biosimilars on the market than the two with which it began.

A Supreme Court ruling on the patent information exchange and launch notification provisions in the Biologics Price Competition and Innovation Act (BPCIA), as well as hearings and trials in individual patent cases, will be important to determining whether any new biosimilars enter the US market this year and, if so, how quickly.

And a wildcard is the impact, if any, on the BPCIA's biosimilar regulatory and legal provisions resulting from the Republican-led Congress and Trump Administration's efforts to repeal and replace the measure's parent legislation, the Affordable Care Act (ACA).



FDA's Review Queue

FDA licensed three new biosimilars in 2016, bringing the total number of products approved under the 351(k) pathway to four. *(See timeline).*

However, just one of the three new products reached market during the year. *Celltrion Inc.*'s *Inflectra* (infliximab-dyyb), a biosimilar to *Janssen Biotech Inc.*'s *Remicade* (infliximab), was

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launched by *Pfizer Inc.* in November. It joined *Sandoz Inc.*'s *Zarxio* (filgrastim-sndz) as the only biosimilars on the US market.

Based upon the publicly disclosed applications currently in FDA's review queue, at least five biosimilars could be approved in the coming year on first-cycle review. The potential new products include the second biosimilar for a single reference product, and the first two biosimilars of targeted cancer agents *(see chart)*.

351(k) Applications Under First-Cycle Review

Goal Date	Proposed Biosimilar	Reference Product
January 2017	Samsung Bioepis' SB2	Janssen Biotech's *Remicade* (infliximab)
June 2017	Coherus' CHS-1701	Amgen's *Neulasta* (pegfilgrastim)
September 2017	Mylan and Biocon's MYL-1401O	Genentech's *Herceptin* (trastuzumab)
September 2017	Amgen and Allergan's ABP 215	Genentech's *Avastin* (bevacizumab)
September 2017 (estimated)	Boehringer Ingelheim's BI 695501	AbbVie's *Humira* (adalimumab)

Much attention will be paid early on to the status of *Samsung Bioepis Co. Ltd.*'s SB2, which if licensed would become the second biosimilar referencing Remicade. The application's user fee goal date is in January, although a three-month extension is always a possibility.

FDA has not convened an advisory committee meeting for SB2, which could be interpreted in two ways. Review staff have said they do not expect to hold public reviews for subsequent 351(k) applications for a given reference product unless they raise scientific issues that warrant public discussion. However, the agency also is reluctant to proceed with an advisory committee review if a sponsor's analytical data do not support a finding of high similarity to the reference product, in which case a complete response letter would be the outcome. (Also see "*Biosimilar Advisory Committee Reviews: Necessity Or Nuisance?*" - Pink Sheet, 20 Jul, 2016.)

If Samsung's SB2 is approved, there could be two biosimilar versions of Remicade on the US market in the second half of 2017.

Even if approved in January, Samsung would not be able to launch SB2 until July at the earliest pursuant to current case law interpreting the BPCIA's launch notification provisions. This timeline sets up the possibility that there could be two biosimilar versions of Remicade on the US market come the second half of 2017, which would be expected to put downward pricing pressure on both Remicade and Inflectra.

An advisory committee review would be expected for Coherus' CHS-1701, a proposed biosimilar to *Amgen Inc.*'s *Neulasta* (pegfilgrastim). However, this milestone has not been reachable for other proposed pegfilgrastim biosimilars that have come before the agency.

Apotex Inc.'s proposed Neulasta biosimilar is believed to have received a complete response letter in 2015 without the benefit of an advisory committee. FDA also skipped the public review process for Sandoz Inc.'s application, which received a complete response letter in July. Sandoz must conduct an additional study and does not expect to resubmit the application until at least 2018. (Also see "*Biosimilars: Sandoz Pegfilgrastim Review, Amgen Adalimumab Launch Extended To 2018*" - Pink Sheet, 28 Oct, 2016.)

The pending applications for *Mylan NV* and *Biocon Ltd.*'s MYL-1401O, and Amgen and *Allergan PLC*'s ABP 215, represent the first proposed biosimilar competitors to *Genentech Inc.*'s blockbuster oncology agents *Herceptin* (trastuzumab) and *Avastin* (bevacizumab), respectively. Both are surely headed to advisory committees, assuming FDA does not first hand the sponsors a complete response letter.

Boehringer Ingelheim's BI 695501, which is seeking to become the second biosimilar of *AbbVie Inc.*'s *Humira* (adalimumab), was a late-announced entry in the review queue, with the company disclosing Jan. 18 that the 351(k) submission had been accepted by FDA.

Will The Missing Applications Resurface?

It remains to be seen whether the coming year will be one of regulatory re-emergence for several early applications that failed to pass muster with FDA in their first go-around.

In addition to Apotex's pegfilgrastim product, this group includes the company's proposed biosimilar of Amgen's *Neupogen* (filgrastim), and *Hospira Inc.*'s (now Pfizer) proposed biosimilar to epoetin alfa (Amgen's *Epogen*/*Janssen Products LP*'s *Procrit*).

The Hospira application received a complete response letter in October 2015, at which time Pfizer said it expected to resubmit the BLA in the first half of 2016. However, the big pharma has since gone quiet on the application's status.

In a December interview, Diem Nguyen, regional president of North America for Pfizer Essential Health, said only that the company is in active engagement with FDA based on the agency's

additional requirements for the application. *(Keep up to date on biosimilars under FDA review with the Pink Sheet Performance Tracker.)*

For FDA, Review Changes On The Horizon …

FDA's biosimilar reviews to date have proceeded under a 10-month review goal timeline. However, that is expected to change on Oct. 1, 2017.

Biosimilar applications submitted on or after that date would be reviewed under a 12-month clock – similar to the PDUFA V "Program" model adopted for new molecular entities and novel biologics – under the BsUFA II agreement.

The hope is that the additional two months of review time, coupled with increased agency/sponsor interactions before and during the review process, will result in fewer review date extensions and complete response letters, and more first-cycle approvals. However, it remains to be seen if this model can do for biosimilar reviews what it did in the novel drug space in terms of enhancing application completeness and review efficiency. (Also see "*Biosimilars Will Get PDUFA-Style Reviews Under New User Fee Plan*" - Pink Sheet, 28 Sep, 2016.)

The BsUFA II agreement also would provide a massive funding boost for biosimilar regulation and review activities, including enhancing the agency's capacity for guidance development and educational initiatives in the space. (Also see "*Biosimilar User Fee Agreement Offers FDA Funding Boost, Fee Structure Overhaul*" - Pink Sheet, 16 Sep, 2016.) Among the guidance documents anticipated are a draft on statistical considerations for analytic similarity data, targeted for release by the end of 2017. (Also see "*Biosimilar User Fee Agreement Puts FDA On Hook For Delayed Guidances*" - Pink Sheet, 22 Sep, 2016.)

However, thanks to a flurry of FDA action in the last few weeks of the Obama Administration, the agency already knocked several guidance documents off the commitment letter's to-do list, including final documents on clinical pharmacology data and nonproprietary naming of biologic products, both of which were targeted for release by May 2019.

… But Interchangeability Guidance Is Finally Behind It

In the biosimilar policy-making space, nothing drew the industry's attention more than the Jan. 17 release of a draft guidance on interchangeability considerations, a document stakeholders have long sought but that has been much delayed. (Also see "*FDA's Document Dump: Guidance Release Skyrockets Ahead Of Trump's Arrival*" - Pink Sheet, 22 Jan, 2017.)

"Hurray, it's finally here," cheered Kay Holcombe, senior vice president of science policy at the Biotechnology Innovation Organization.

The guidance "is considered to be a key to getting uptake of biosimilar products in the

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marketplace" and ensuring public confidence that such products have been demonstrated to be interchangeable with their reference products, Holcombe said. "It's a really important step forward in the goal of BPCIA to get biosimilar products available to patients and more options available to prescribing providers."

Although the agency has been providing one-on-one advice to sponsors about the types of data it expects to see for interchangeability, the draft guidance formally lays out these evidentiary expectations for all biosimilar developers, including those who have not yet had such discussions with the agency, as well as non-industry stakeholders.

For example, the draft makes clear that FDA expects data from a multiple-switch study to support a demonstration of interchangeability. (Also see "*Biosimilar Interchangeability: How To Design A Multiple-Switch Study*" - Pink Sheet, 18 Jan, 2017.)

The guidance should help industry make more informed decisions about the resources needed for developing an interchangeable, while also making the development process itself more efficient, industry representatives said.

> ***With FDA's guidance, the biosimilars industry now has a target on interchangeability, Biosimilars Council's Liang said.***

"When there's no target, there's nothing to shoot at," said *Pfenex Inc.* CEO Bert Liang, who chairs the Generic Pharmaceutical Association's Biosimilars Council. "Now we've got a target" and can plan development programs accordingly.

[Editor's note: Liang resigned as CEO of Pfenex on Jan. 24.]

Kimberly Greco, director of global regulatory and R&D policy at Amgen, noted that when sponsors meet with the agency they have a limited amount of time to discuss numerous matters.

"You've got all these questions you want answered," Greco said at the FDA/CMS Summit in December. "If more of those questions are answered by way of a guidance that's already in place, it just makes the whole process more efficient."

The guidance also should help clarify public perceptions and misunderstandings about the

products approved under the 351(k) pathway given confusion among healthcare providers and patients, among others, over the terminology of biosimilars.

"There's a lot of confusion between what is an interchangeable product, what is automatic substitution as well as what is a switch," said Pfizer's Nguyen said.

The agency is requesting comments on the guidance, and other issues related to interchangeability and lifecycle regulation of biosimilars, by March 20.

One provision that may draw some industry objections is FDA's recommendation that the comparator used in switching studies be the US-licensed reference product rather than one approved in a foreign market. (Also see "*Make Interchangeability Great Again: Biosimilar Switching Studies Need US Comparators*" - Pink Sheet, 18 Jan, 2017.) Some biosimilar developers may try to make the case for establishing a bridge between an EU-approved reference product and a US-licensed reference product for purposes of demonstrating a biosimilar's interchangeability.

The first request for interchangeability, and the first approval, will be landmark events, although it's difficult to predict when such milestones might occur.

"I think the first one to get interchangeability regardless of [whether] it has competitors or not, it's going to be huge," Molly Burich, Boehringer Ingelheim's associate director of public policy for biosimilars, pipeline and reimbursement, said at the FDA/CMS Summit in December. "It's going to be really important for the market because that will be another ... step. Just as the first approval was a big step and just as the first pharmacy benefit product that's approved versus medical benefit – those are all steps along the way."

Supreme Court Will Judge The 'Dance'

Legal proceedings also promise to figure prominently into the biosimilar market development in 2017, with the land's highest court expected to have a major impact.

The Supreme Court's decision to hear a dispute between Amgen and Sandoz involving Zarxio should provide much needed clarity for both reference product sponsors and biosimilar developers as to whether the BPCIA's "patent dance" is optional or mandatory, and whether 351(k) sponsors must wait until licensure before providing 180-notice of launch. (Also see "*Supreme Court Jumps Into Biosimilars Battle Over Launch Notification, Patent Dance*" - Pink Sheet, 14 Jan, 2017.)

Robert Cerwinski, a partner at Goodwin Procter, noted that with only a relatively small number of biosimilar-related patent cases pending, the high court's decision will provide an early clarification of the statute. "I think it would tend to avoid chaos rather than create it," he said.

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However, Cerwinski expects to see litigation between reference product and biosimilar sponsors ramp up in the coming year.

Besides the Supreme Court's ruling in the Zarxio case, "the other big story in 2017 is the sheer number of BPCIA litigations we're going to see," he said. The increasing number of 351(k) submissions is going to lead to "the vigorous litigation wrangle we've been predicting for the past two years."

Such litigation will be nothing if not complex, Cerwinski said, pointing to the "patent thicket" that AbbVie has established around Humira.

> ***"Patents remain the biggest obstacle to biosimilars becoming a larger force in the market." – Lowenstein Sandler's Shehan***

In June, AbbVie sued Amgen asserting that *Amjevita* (adalimumab-atto) infringes 10 Humira patents. However, AbbVie believes the biosimilar infringes a total of 61 patents covering Humira, meaning that a second wave of litigation is expected. (Also see "*AbbVie v. Amgen Round One: Humira Biosimilar Infringes 10 Patents, Suit Claims*" - Pink Sheet, 5 Aug, 2016.)

The schedule and sheer complexity of the Humira patent dispute between AbbVie and Amgen will be a good barometer of the litigation to come with other biologics, Cerwinski said, noting there are going to be many more biosimilars in development that will have to contend with more than 10 reference product patents. "I think that's going to be typical going forward, especially if AbbVie achieves success with its patent thicket strategy."

Given the complexity and pace of the Humira patent litigation, Amgen has said it does not expect to launch Amjevita, approved by FDA in September 2016, until at least 2018.

Thus, even if the Supreme Court were to decide that biosimilar launch notification can be provided ahead of product licensure, there's no guarantee that products would get onto the market any sooner given the complicated patent litigation that is beginning to evolve in this space.

"The patents remain the biggest obstacle to biosimilars becoming a larger force in the market," said James Shehan, senior counsel at Lowenstein Sandler.

A near-term launch of another approved biosimilar, Sandoz's *Erelzi* (etanercept-szzs), also seems unlikely given ongoing patent litigation with Amgen and *Roche* related to *Enbrel* (etanercept) patents. A claim construction hearing will take place in February, with a trial scheduled for April 2018.

Another near-term legal proceeding to watch is the February trial involving Janssen's cell culture media patent for Remicade. Although Celltrion and Pfizer's Inflectra has already entered the US market, the verdict could have important ramifications for the two companies if they are required to pay damages to Janssen. Conversely, an adverse verdict for Janssen could negatively impact its ability to keep other biosimilar versions of Remicade at bay, such as Samsung's SB2.

A Little Thing Called Repeal And Replace

No look ahead at the regulatory, legal and commercial landscape for biosimilars in 2017 would be complete without addressing the possibility of legislative changes to the BPCIA and the Trump Administration's impact on medical product regulation in general.

The BPCIA was enacted in 2010 as part of the ACA, the massive health care reform law that the Republican-led Congress and new administration are determined to repeal, with or without a replacement. While the BPCIA was a small, discrete section of the massive ACA, the reopening of the health care reform bill could create an opportunity for changes to the BPCIA provisions.

A wholesale overhaul of the BPCIA is not anticipated, and many observers remain skeptical that its provisions will be touched in any ACA repeal-and-replace effort.

Despite all the acrimony over the ACA, the BPCIA is not much of a political football, Cerwinski said. "Our current thinking is it's pretty low risk that the BPCIA is going to be repealed or reworked as part of this political exercise."

Goodwin Procter Partner Scott Lassman said the BPCIA is not very controversial, particularly compared to the broader ACA. "I'm not hearing people say they want to get rid of it as part of the ACA, but unfortunately it's part of that overall bill," Lassman said. "Anytime you open up a bill like that, you never know what's going to happen."

The Trump Factor

Industry and FDA also will be holding their breath that the BsUFA II agreement and other negotiated user fee programs move smoothly through Congress and are signed into law by President Donald Trump well ahead of their Sept. 30 expiration. (Also see "*PDUFA VI: Industry Ready For 'Hard Sell' To Keep Agreement Intact*" - Pink Sheet, 19 Dec, 2016.) Whether and how FDA's hiring for user fee-funded positions under these various agreements might be affected by the new administration's federal hiring freeze will be a concern for agency and industry alike.

Another uncertainty is what kind of impact the new administration might have on FDA's review activities.

President Trump has not yet announced his pick to lead FDA, although the prospects for a leadership transition, and some of the names floated as potential commissioner nominees, have generated anxiety and uncertainty among agency staff. (Also see "*Woodcock Tries To Calm US FDA Staff Fears About Trump*" - Pink Sheet, 21 Dec, 2016.)

Industry also is concerned about how the leadership transition will impact the agency's operations.

> ***If the Trump Administration "is true to its comments to deal with drug prices, biosimilars seems like a logical place for them to put some effort into and prioritize." – Zuckerman Spaeder's Angulo***

Gillian Woollett, senior vice president at Avalere Health, said her most important concern is confidence in the science around biosimilars. Historically there has been deference to FDA on scientific matters, Woollett said, questioning how the change in administration might impact that deference.

"The stability of the staff given the many years that it takes to develop any product becomes really important," Woollett said. "The continuity of the review staff matters a great deal."

Carlos Angulo, a partner at Zuckerman Spaeder, suggested that the potential for biosimilars to reduce healthcare costs could protect FDA's operations from political meddling, or even give them a boost.

"Biosimilars hold such promise and if the [Trump] Administration is true to its comments to deal with drug prices, biosimilars seems like a logical place for them to put some effort into and prioritize," Angulo said. "Whether that actually happens or not, we don't know."