Pink Sheet
pink.pharmamedtechbi.com Vol. 79 / No. 5 January 30, 2017
Pharma intelligence informa

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

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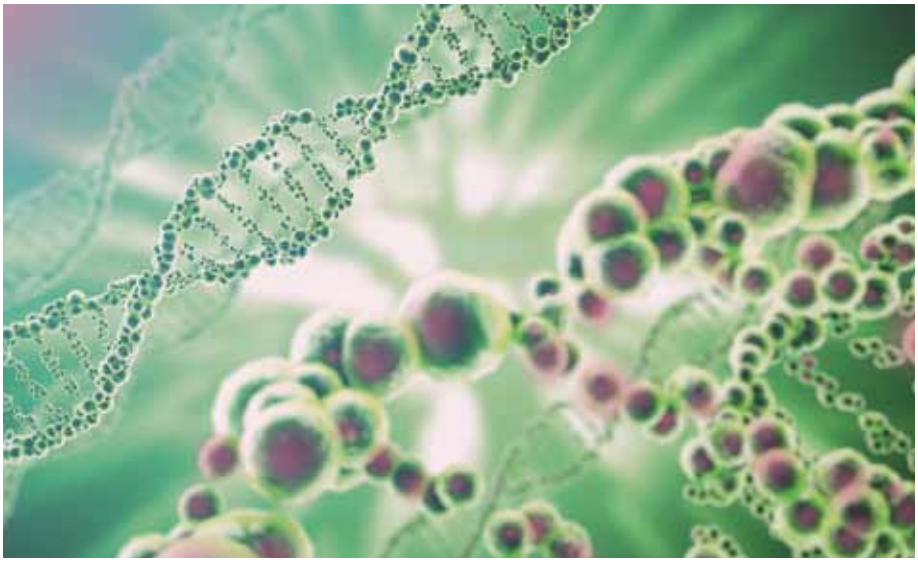

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The US FDA's frenetic pace of regulatory activity in the Obama Administration's waning days may raise concerns that agency efforts to implement the biosimilar approval pathway could hit a lull in the coming months.

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.

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FDA can expect to face a barrage of comments on its recently released draft guidance on interchangeability considerations, but when it might be tasked with making its first designation remains a question.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

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UK Favors Post-Brexit EMA/MHRA 'Mutual Recognition' Deal

http://bit.ly/2k6IQ5l

Jeremy Hunt, the UK Secretary of State for Health, has told a parliamentary committee that the EMA is likely to leave the UK but that his government will be seeking a close relationship with the agency that could involve the mutual recognition by the UK regulator of EU drug approvals.

J&J Outlines Pricing Transparency Plan, Will Others Follow?

http://bit.ly/2kyndfj

CEO Gorsky describes J&J's approach to drug pricing and pledges to provide more detail in an annual transparency report. Investor pressure regarding the pricing debate continued during the Novartis earnings call. Value arguments expected to dominate pharma's message.

FDA Commissioner Candidate Gulfo Hates Breakthrough, Wants To Reevaluate User Fees

http://bit.ly/2jWoZnl

In an interview, Joseph Gulfo, former medtech industry CEO and vocal FDA critic, outlines his worldview and interest in pushing aggressively against increasing the FDA 'body of law.'

NIH Director Collins Stays On: Continuity For 'Moonshot' – And Barrier To 'March In'

http://bit.ly/2jk0SNM

For industry, the sole health agency head held over from the Obama Administration means the 'Moonshot' priorities will move forward – and one possible threat to pricing is cut off.

New Policy Fund Reflects Korea's Commitment To Health Biotech

http://bit.ly/2jCx1kl

South Korea's plan to create a policy fund to support new growth engine industries seems to reaffirm the government's unwavering commitment to nurture the biotech and health care sectors despite the ongoing political chaos in the country.

inside:

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petition 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, p. 5)*.

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 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*).

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.

> 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.

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

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)

U.S. BIOSIMILARS: The Last 12 Months In Review And A Look Ahead

2016

February 9 - FDA advisory committee review of Celltrion's Inflectra

February 16 - Sandoz petition requesting Supreme Court review of 180-day launch notice for Zarxio

April 5 - Inflectra (infliximab-dyyb) approved

August 30 - Erelzi (etanercept-szzs) approved

October 20 - Public meeting on BsUFA II agreement

December 27 - US Solicitor General brief supporting Supreme Court review in Zarxio litigation

December 28 - Final guidance on clinical pharmacology data

March 11 - FDA draft guidance on implementation of BPCIA "transition provisions"

March 31 - Draft guidance on biosimilar labeling

July 12 - FDA advisory committee review of Amgen's Amjevita

July 13 - FDA advisory committee review of Sandoz's Erelzi

September 16 - BsUFA II draft agreement released

September 23 - Amjevita (adalimumab-atto) approved

November 21 - Inflectra launched by Pfizer

2017

January 12 - Final guidance on nonproprietary naming

January 13 - Supreme Court grants review in Zarxio litigation of BPCIA "patent dance" and launch notification provisions

January 17 - Draft guidance on interchangeability considerations

September 30, 2017 - BsUFA I program sunsets

December 31, 2017 - Guidance target date: Analytical similarity data statistical considerations (draft)

2018

September 30, 2018 - Guidance target date: Formal meetings between FDA and biosimilar sponsors (revised draft)

2019

March 31, 2019 - Guidance target date: Biosimilar postapproval manufacturing changes (draft)

May 31, 2019 - Guidance target date: Biosimilar labeling (revised draft or final)

2020

March 2020 - BPCIA "transition provisions" take effect

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.

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. Among the guidance documents anticipated are a draft on statistical considerations for analytic similarity data, targeted for release by the end of 2017.

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.

"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 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."

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

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.

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.

"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. 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.

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.

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."

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

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

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.

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. 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.

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

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."

Published online January 24, 2016

Biosimilars Boost In Europe: 2017 Kicks Off With Three Approvals And Backing From ESMO

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Biosimilars in Europe have made a strong start to 2017, with three new drug approvals, backing from the European Society for Medical Oncology, and the first biosimilar anticancer awaiting imminent approval.

Meanwhile, the European Commission has published a new question and answer document explaining the ins and outs of biosimilars for patients, and the European Medicines Agency and the European Directorate for the Quality of Medicines and Healthcare are to hold a joint event on the quality assessment of biosimilars.

In the first two weeks of January, the commission issued marketing authorizations to three biosimilars – just one short of the total number of biosimilars approved in 2016. They are: Gedeon Richter Ltd.'s Terrosa and Stada Arzneimittel AG's Movymia – biosimilar versions of Eli Lilly & Co.'s osteoporosis drug *Forsteo* (teriparatide) – and Merck Sharp & Dohme Ltd.'s *Lusduna* (insulin glargine), a competitor to Sanofi's diabetes product Lantus.

This brings the total number of biosimilar drugs approved in Europe to 25, corresponding to 10 different active substances (or 11 if you count epoetin alfa and zeta separately).

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Moreover, Celltrion Inc.'s *Truxima* (rituximab), a version of Roche's *MabThera* and the first biosimilar anticancer to receive a positive opinion from the EMA's scientific committee, the CHMP, is expected to receive a marketing authorization from the commission within a couple of months. Truxima, which is indicated for non-Hodgkin's lymphoma, chronic lymphocytic leukemia, granulomatosis with polyangiitis, microscopic polyangiitis, and rheumatoid arthritis, received the CHMP green light in December 2016.

The product, which had its first worldwide approval in South Korea in November last year, will be in the vanguard of a new crop of biosimilar versions of major anticancers approaching the European market. Currently under review at the CHMP are two versions

of Roche's *Avastin* (bevacizumab) and three of its *Herceptin* (trastuzumab), and at least one other biosimilar of MabThera.

ESMO SUPPORT FOR CANCER BIOSIMILARS

Great expectations are being pinned on biosimilars as a source of healthcare savings, particularly in the cancer area where treatments are becoming increasingly expensive. With 225 new anticancer drugs expected to be introduced up to 2020, biosimilars are "particularly appealing in view of their promise to reduce the heavy burden faced by healthcare systems worldwide," according to the oncology physicians' body, ESMO.

In a position paper issued on Jan. 16, ESMO describes the approval standards for biosimilars, explains how they can be safely introduced into clinical practice, and outlines the potential benefits for patients and healthcare systems in terms of improving the affordability of cancer treatment in the longer term. Backing from ESMO is important as physician reluctance to prescribe biosimilars is often seen as a barrier to market uptake.

"Biosimilars give us the chance to make treatment options for cancer more affordable everywhere," said ESMO president Professor Fortunato Ciardiello. "Clinicians are starting to ask questions about how to incorporate biosimilars into their daily practice and until now they did not have an authoritative source of information. This paper serves to educate practising physicians on this complex topic."

Professor Josep Tabernero, chair of ESMO's Cancer Medicines Working Group, agreed, saying that biosimilars were "an excellent opportunity to have good, valid drug options that improve the sustainability and affordability of cancer treatment in various countries."

On the financial front, the position paper notes that price reductions for biosimilars are expected to range from 20% to 40%, with potential savings of €50-100bn forecast by 2020. "The majority of monoclonal antibodies are set to come off patent by 2020, which will open the door for biosimilars and could dramatically change the oncology landscape," it says.

The paper also outlines the principles underlying the development and approval of biosimilars, examining current issues such as definition, labeling, extrapolation, switching, interchangeability, and substitution.

With 225 new anticancer drugs expected by 2020, biosimilars are "particularly appealing in view of their promise to reduce the heavy burden faced by healthcare systems worldwide," ESMO says.

Extrapolation to all the clinical indications of the originator drug should be allowed "if verified scientifically", i.e., on the basis of analytical, preclinical, pharmacokinetics, pharmacodynamics and clinical data, along with immunogenicity data, it declares.

Switching too is acceptable provided the switch decision is taken by doctors who have "grasped a deep understanding of the product" and informed the patient, and as long as they monitor the patient in collaboration with nursing teams. "This is crucial as it will allow the physician and their colleagues to trace any adverse events to the appropriate product."

It notes that interchangeability is linked to substitution, which is a competence of the 28 EU member states, and says that automatic substitution by pharmacists should be avoided. It notes nine of the 28 countries "completely prohibit" automatic substitution by the pharmacist, while six restrict substitution to "ensure the safety of patients and in particular, avoid unforeseen immune responses."

GROWING SUPPORT

Regulatory backing for biosimilars in Europe has been growing steadily over the past few years as more evidence on their use accumulates. The Dutch agency came out in support of biosimilar switching in 2015, and others followed suit, the latest being the Italian regulator AIFA (in December 2016).

Also last year, the Norwegian NOR-SWITCH study involving Johnson & Johnson's Remicade and biosimilar infliximab supported the biosimilar concept by showing that switching can be undertaken on the basis that there are no meaningful clinical differences between biosimilars and their reference drug – at least according to the biosimilars industry. The R&D industry was more circumspect, pointing out that the study did not address multiple switching and questioning the pooling of endpoints.

Biosimilar-related issues are also discussed in a new Q&A document just issued by the commission, entitled "What I need to know about biosimilar medicines. Information for patients." The document first appeared in 2013 as part of a 43-page consensus information document entitled "What you need to know about biosimilar medicinal products."

The new document is intended to "empower patients with reliable information on the use of biosimilar medicines as an alternative therapeutic option," according to a joint press release from the generics and biosimilars trade body Medicines for Europe, the European industry federation EFPIA, and the biotech industry association EuropaBio.

They also note that for the third year in a row the commission is organizing a multi-stakeholder workshop on biosimilars, which will take place on May 5, 2017.

EMA/EDQM BIOSIMILARS EVENT

Meanwhile, the role of the European Pharmacopoeia (PhEur) in the assessment and marketing authorization of biosimilars is to be discussed at a joint EMA/EDQM event on Feb.8 in Strasbourg, France.

The event will include an overview of the EU regulatory framework and the role of the EMA, how the PhEur fits into this framework in terms of the role and application of pharmacopoeial monographs, and a presentation on quality assessment of biosimilars from an EU regulator.

It will take place together with a PhEur training session on biologicals looking at topics like the proper use and interpretation of texts relevant to biologicals, and the use of PhEur reference standards.

From the editors of Scrip Regulatory Affairs. Published online January 24, 2016

Why Baxter's GMP False Claims Settlement Was Smaller Than Those Of GSK, Ranbaxy

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The nearly $18.2m settlement with Baxter Healthcare Corp. that the Justice Department announced Jan. 12 pales in comparison to the only other GMP false claims settlements, the $750m settlement in October 2010 with GlaxoSmithKline PLC and the $500m settlement in May 2013 with Ranbaxy Laboratories Ltd.

As with the first two, the Baxter settlement included payment for both criminal and civil charges, but with relatively more emphasis on the criminal aspect.

Baxter agreed to pay an $8m criminal fine and forfeit another $8m for selling adulterated drugs. In addition, the company agreed to a deferred prosecution agreement under which it could escape a criminal misdemeanor charge if it undertook certain specified quality improvement measures in a timely fashion.

The civil False Claims Act element was much smaller in the Baxter case, accounting for only $2.2m. The relator in the case, Christopher Wall, and his legal team got less than $432,000 of the civil settlement. Wall was represented by two Charlotte, NC, lawyers, Anthony Scheer and Thomas Odom.

Another difference between the Baxter case and the others: as an HVAC technician, Wall had a limited view of the way Baxter was conducting operations at the North Cove plant near Marion, NC, where he worked. The whistleblowers in the GSK and Ranbaxy cases were high-level officials who had global perspective of their companies.

What Wall saw that no one in authority could see was that there was mold on cleanroom air supply filters, and that the filters needed to be changed.

ROLE OF TERMINAL STERILIZATION

Yet another difference: while the other cases spawned recalls, seizures, import alerts and withdrawal of application approvals, the Baxter case did not.

Instead, repeated throughout Baxter settlement documents is a statement that mold levels never exceeded the limits set in environmental monitoring plans on file with FDA and incorporated into the FDA approvals for the drugs manufactured at the North Cove plant.

Additionally, the documents say that mold was never found to exceed limits set for pre-sterilized product, and endotoxins were never found to exceed limits in post-sterilization product.

The documents state that mold cannot survive at 250 degrees F, the temperature at which the plant sterilizes all product.

WARNING LETTER WAS HARSHER

FDA had taken a much harsher position on environmental monitoring and terminal sterilization in a May 2013 warning letter that was related to the whistleblower's allegations.

"There was no scientific justification for the sampling plans utilized for environmental monitoring in areas that your firm uses to manufacture terminally sterilized injectables," the warning letter said.

The agency went on to say that the environmental monitoring program was insufficient to detect contamination of concern, such as the mold seen on the clean side of filters for the sterile filling area's air supply.

The warning letter went on to sharply criticize Baxter's reliance on terminal sterilization to protect patients.

FDA said that in Baxter's response to observations made in a November 2012 inspection, "you downplay the product quality and safety impacts posed by the mold observed on the clean side of HEPA filters supplying air to your sterile filling areas on the grounds that products made in these areas are terminally sterilized."

The agency added that the company should protect sterile products from microbiological contamination during processing even if they will be terminally sterilized, "in order to minimize sterilization challenge and byproducts of excessive bioburden."

GSK SETTLEMENT

In the first GMP false claims settlement, GlaxoSmithKline in October 2010 agreed to pay $750m to resolve whistleblower allegations brought by Cheryl Eckard, a former global quality assurance manager, regarding quality issues at a plant in Cidra, Puerto Rico, operated by GSK's SB Pharmco unit.

The settlement included $150m for criminal charges and $600m for civil charges – of which Eckard and her legal team received $96m.

That case hinged on a report Eckard presented to GSK executives in April 2003 documenting a history of GMP violations throughout 2002 and 2003. The following month, the company terminated her employment. She later took the report to FDA and in 2004 filed a qui tam suit under the False Claims Act, the first ever for GMP issues.

A variety of GMP issues that FDA said could pose risk to consumers factored into that case, including microbial contamination of *Bactroban* ointment, poor content uniformity of *Avandamet* tablets and *Paxil CR* tablet splitting problems. SB Pharmco did not recall the Bactroban until pressed by FDA and failed to recall all of the Avandamet and Paxil CR, eventually leading to product seizures.

GSK closed the plant in 2009.

Related litigation continues. In November, a federal court judge in Pennsylvania denied GSK's motion to dismiss a case brought by 41 private insurers alleging GSK sold them billions of dollars of worthless, adulterated drugs made at the Cidra plant.

RANBAXY SETTLEMENT

In the second GMP False Claims Act settlement, Ranbaxy agreed in May 2013 to pay $500m to resolve allegations of data fraud and drug manufacturing violations.

The Ranbaxy settlement included a $130m criminal fine, a $20m

forfeiture and $350m for civil claims brought under the False Claims Act and related state laws.

Nearly $49m of the civil settlement went to the relator in that case, Dinesh Thakur, and his legal team. Thakur had worked at Ranbaxy for nearly two years as director of project and information management.

The allegations in that case were that Ranbaxy had falsified bioequivalence, stability, dissolution and other testing results, both in support of generic drug applications and to show GMP compliance.

One consequence was that in September 2008 FDA added 26 Ranbaxy drugs and seven active substances to its drug GMP import alert, preventing them from continuing to reach the US market.

Another consequence was that the agency withdrew approval of 27 abbreviated new drug applications. As part of a related consent decree announced in January 2012, Ranbaxy agreed to never again submit applications for those drugs.

From the editors of Gold Sheet. Published online January 26, 2016

The Case of Baxter's Moldy HEPA Filters

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The case of a Baxter Healthcare Corp. site's moldy cleanroom air filters is a cautionary tale involving the kind of quality culture issues that could bedevil any large pharmaceutical manufacturing facility looking to stay out of trouble with the US FDA.

There were organizational siloes, professional blinders and missing procedures. There were basic misunderstandings and a lack of trust. There was even the standard all-hands meeting where the site's top official appeared to set the tone for a strong quality culture that never quite materialized.

As the months went by, various plant personnel missed one opportunity after another to confront a mold problem in a series of missteps that the federal government prepared to prosecute as a corporate crime.

The Baxter site's quality culture struggles were on display in a statement of facts that the Justice Department filed Jan. 12 with the US District Court for the Western District of North Carolina as part of an $18m criminal and civil False Claims Act settlement, and in a warning letter FDA sent the company six months after the inspection that brought the crisis to a head.

At the heart of the case is the story of a maintenance technician who couldn't stop worrying about mold he saw.

THE JULY 2011 SHUTDOWN

The trouble began in July 2011 during the annual shutdown of the Line 11 cleanroom at Baxter's 1.4 million-square-foot North Cove manufacturing facility, nestled in the valley of the North Fork Catawba River near Marion, NC.

The North Cove plant, the largest of its kind in the world, produced 1.5 million bags of sterile intravenous solution per day on its 12 lines, supplying 60% of the IV bags used in US hospitals.

When it was up and running, workers filled 300,000 IV bags a day in the Line 11 cleanroom, about 20% of the IV bags made at North Cove and 9% of the IV bags used in the US.

But on this day, Line 11 was down and two of the plant's 2,000 employees were in the cleanroom inspecting and testing the integrity of 120 high efficiency particulate air filters arrayed across its ceiling, one by one.

Baxter's North Cove plant is nestled in the valley of the North Fork of the Catawba River in western North Carolina. Source: Google Earth

The test involves connecting a portable aerosol generator to an air supply duct, and using it to drive a steady flow of poly alpha olefin aerosols toward a HEPA filter, then passing a handheld receptor probe in overlapping strokes across the filter surface to detect any gaps large enough to let the aerosol particles through.

The purpose of the test is to make sure the filter would not allow particles such as mold spores into the cleanroom.

Of course, if there is mold growing on the inner surface of the filter, then air flowing through the filter could blow mold particles into the cleanroom even if the filter is leak free.

But while there was a standard operating procedure at the North Cove plant to replace leaky HEPA filters, there was not one for replacing stained or moldy ones, although maintenance workers often replaced them anyway.

WHAT WAS BEHIND THE GRATES

The two heating, ventilation and air conditioning technicians had to remove ceiling grates before they could test the HEPA filters that were over Line 11's belts A, B, C and D.

When they removed the grates, they saw stains on 15 of the fil-

The 1.4 million-square-foot Baxter North Cove plant is the largest of its kind in the world. Source: Google Earth

The plant draws air from above through HEPA filters for its manufacturing lines. Source: Google Earth

ters. It looked like mold was growing on them.

One of the HVAC technicians, Christopher Wall, showed one of the stained HEPA filters to his second-line supervisor, the superintendent of utilities. Then Wall and his colleague, who has not been publicly identified, began replacing the apparently moldy filters.

They kept replacing the stained filters until their boss, the HVAC supervisor, told them to stop. At that point, five moldy-looking HEPA filters remained in the ceiling, some of them directly above filling equipment. But the possible mold was no longer visible after Wall and his colleague reattached the ceiling grates.

WHAT THE RECORDS MEANT

Wall's colleague wrote in the maintenance record that they'd changed certain filters prior to testing "due to discoloration." Wall added: "Filters also had mold."

When mid- and upper-level managers reviewed and approved these records, they assumed that all of the discolored, apparently moldy filters had been replaced.

The only person in the plant's quality organization to review the records was the quality critical systems engineer. He complained to the superintendent of facilities and his boss, the director of facilities, that Wall should not have used the word "mold" in the records because the HEPA filters had not been tested for mold.

The critical quality systems engineer had a point. And perhaps for this very reason, the plant had a policy dating back to 2006 against using the word "mold" in HEPA filter maintenance paperwork.

But then no one ever tested the filters for mold. That wouldn't happen until FDA got involved.

THE ALL-STAFF MEETING

Late that October, the plant manager convened a plant-wide meeting where he emphasized that employees should come to him with any quality concerns they may have.

After the meeting, Wall approached the plant manager and told him about the five apparently moldy HEPA filters in the Line 11 cleanroom – and that he feared his supervisors would retaliate against him for reporting about the filters.

The manager asked the human resources director to investigate Wall's complaints, which she did over the next two months.

But the HR director treated it as a personnel matter rather than a quality issue, and never brought it to anyone's attention in the plant's quality organization.

Wall drew her a map showing the five HEPA filters' locations; she gave it to the director of facilities, keeping a file copy.

As a result of Wall's report to the plant manager, the HVAC supervisor who had forbidden him from replacing the filters had to inspect the filters. The supervisor concluded that they were not as dirty as other filters in the cleanroom, and would not be replaced until the line's next annual maintenance shutdown in July 2012.

THE JULY 2012 SHUTDOWN

When Wall and his colleague removed the ceiling grates for the July 2012 maintenance shutdown, they saw what looked like mold on 29 HEPA filters over belts A, B, C and D.

Wall showed the stained filters to the maintenance critical systems engineer, who immediately stepped outside to confer with the superintendent of utilities and the director of facilities. The superintendent walked away to place a call, and the director told him to have the HVAC technicians "wipe it off."

The engineer relayed the order, taking it to mean wiping off the grates because wiping off the filters would damage them. The workers did not follow his instructions because it was impossible to wipe stains or mold from HEPA filters.

The HVAC supervisor then instructed Wall to only replace leaky filters, not stained or discolored ones. So as they had the year before, he and his colleague reattached ceiling grates over moldy filters.

QUALITY GETS INVOLVED

Wall wrote about the apparent mold in the maintenance records for the July 2012 shutdown.

When the critical quality systems engineer saw these comments, he did not rebuke the maintenance organization for using the word "mold" in the records, as he had the year before. Instead he showed the comments to his supervisor, the laboratory services quality manager, who in turn showed them to the director of quality.

The quality director told the laboratory services quality manager to have the filters inspected and, if moldy, replaced.

These instructions were relayed via the quality critical systems engineer to the superintendent of facilities and the HVAC supervisor.

Meanwhile, the HR director got wind of Wall's latest complaints about mold and launched a new investigation into them.

HOW THE FILTERS WERE CLEAN

In late July the HVAC supervisor and two HVAC technicians conducted the inspection the quality director requested, using a map provided by the superintendent of utilities that showed which of Line 11's 120 HEPA filters to inspect.

Wall's colleague and another employee say they told the HVAC supervisor that they were re-inspecting the wrong area, and that Wall and the colleague had never seen mold in the area where they were pulling ceiling grates.

When they were finished, the HVAC supervisor added a statement to the pages of the maintenance record where Wall had said there was mold: "On 07-29-12, a follow-up inspection was performed on HEPA filters on Filling Line 11. No discoloration was found on the HEPA filters. No HEPA filters were in need of replacement."

The HR director, informed of these findings, concluded that Wall's complaints had been resolved.

THE FDA INSPECTION

FDA investigators arrived unannounced on Nov. 7 and conducted an inspection over the next nine days.

They found numerous moldy HEPA filters above the ceiling grates over belts A, B, C and D in the Line 11 cleanroom. Testing later showed that there were several mold species and other particulates on the filters.

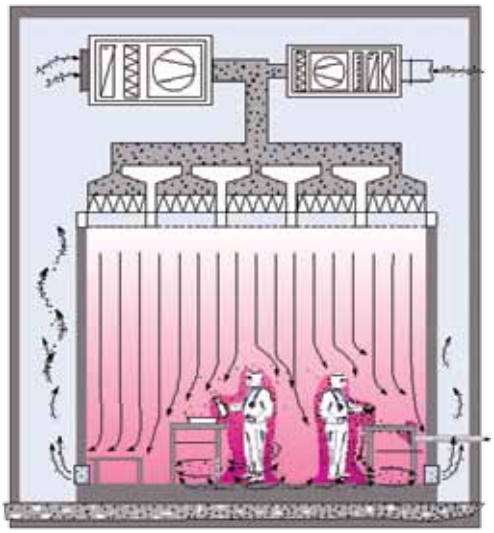
THE WARNING LETTER

A May 2013 warning letter from FDA provided additional detail about the inspection and its aftermath.

A week into the inspection, FDA's investigators found "numerous HEPA filters, HEPA filter supporting grid work, HEPA filter screens, and HEPA filter screen tracks contained varying amounts of discolored areas, chipping paint, multicolored coalescing droplets, and clumps of dark material that FDA testing later revealed was mold" in a fill line, the warning letter said.

The letter notes that Baxter halted production in that line and another for remediation that it completed prior to the issuance of FDA's warning letter. (Wall and his colleague also had replaced stained HEPA filters in Line 10, but without telling anyone in advance.)

FDA nevertheless criticized the firm for failing to say how long the mold had been there. Nor, FDA stressed, had Baxter "identified the root cause that allowed the mold to proliferate to a level of TNTC (Too Numerous to Count) in several environmental samples directly over your filling line."



Air flows down through HEPA filters toward workers and equipment in this depiction of a typical cleanroom. Source: Wikipedia

The agency noted that Baxter promised to set acceptance criteria for discolored or stained HEPA filters, to include representatives from its quality organization in inspections of the filters on all fill lines, and to escalate any quality-related issues into its environmental deviations process.

THE DEFERRED PROSECUTION AGREEMENT

As part of the Jan. 12 settlement, the Justice Department and FDA deferred prosecution of a misdemeanor charge for introducing an adulterated drug into interstate commerce for the 30 months that remediation was expected to require, after which the government would seek dismissal. However, if remediation takes longer, the deferred prosecution agreement will likely be extended.

To win conditional release from criminal liability, Baxter agreed to pay an $8m penalty, forfeit an additional $8m of proceeds, and to up its game on quality.

THE ENHANCED COMPLIANCE PROGRAM

An attachment to the deferred prosecution agreement spells out the enhancements Baxter will have to make to its quality compliance program to avoid criminal prosecution.

The plant will have to:

- Step up its efforts to prevent, detect and respond to mold, and to communicate about it both internally and with FDA;
- Seriously upgrade its corrective and preventive action program;
- Strengthen its handling of employee concerns; and
- Add annual reviews by the president of Baxter's hospital products business and by the company's board of directors.

From the editors of Gold Sheet. Published online January 26, 2016

Bristol, AstraZeneca Changes To IO Strategy Could Ultimately Be Regulatory Gain

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Bristol-Myers Squibb Co.'s announcement that it will not seek accelerated approval of its Yervoy/Opdivo combination in first-line lung cancer has disappointed investors and seems to concede a significant edge to competitor Merck & Co. Inc., but it may make more sense from the regulatory perspective, giving the company a better chance for a successful filing.

Bristol announced Jan. 19 that it was not going to seek accelerated approval for the combination of its PD-1 inhibitor *Opdivo* (nivolumab) with the company's CTLA-4 inhibitor *Yervoy* (ipilimumab), contrary to prior suggestions that the accelerated pathway was viable. The company said the decision was based on "a review of data available at this time."

"In order to protect the integrity of ongoing registrational studies, the company will not be providing additional details," Bristol's statement read.

Analysts were frustrated by the brief announcement, which left more questions than answers.

It's been unclear what data the company would have used to support an accelerated filing. Data from the randomized Phase III CheckMate 227 study of the combination are due in the first quarter of 2018, though interim analyses are expected ahead of that. The single-arm, open-label Phase II CheckMate 568 study of the combination in PD-L1-positive first-line lung cancer has been ongoing and provided a likely potential vehicle for accelerated approval. That study is set to enroll 590 patients and has objective response rate as the primary endpoint.

MERCK IN THE LEAD

The decision leaves competitor Merck in an advantageous position as FDA accepted a filing for accelerated approval of its combination of *Keytruda* (pembrolizumab) with chemo in first-line lung cancer with a user fee date of May 10. Merck's filing is supported by randomized data from the Phase II KEYNOTE-021 study in which the combination demonstrated better progression-free survival and objective response rates. Results from the Phase III KEYNOTE-189 trial are expected this year.

> Bristol had some good news: it is gaining $625m plus royalties under a settlement with Merck over PD-1 patent litigation.

Keytruda is already approved as a monotherapy for patients with first-line lung cancer with high PD-L1 expression whereas Bristol's plans to get Opdivo approved as a monotherapy for first-line use faded with the failure of the CheckMate 026 study, initially in patients with lower levels of PD-L1 expression, but ultimately failing in patients with higher levels as well.

Merck now clearly has the first-mover advantage in the most valuable indication for checkpoint inhibitors – first-line non-small cell lung cancer (NSCLC) – and dominating the frontline space will have knock-on effects for the second-line market as prescribers don't see a role for second-line PD-1 after PD-1 up front.

Bristol's share price was down by 11.28% on Jan. 20, closing at $49.23, but the company did have some good news before the end of the day. Bristol and its partner Ono Pharmaceutical Co. Ltd. announced a settlement with Merck on all patent-infringement litigation related to Keytruda. Per the agreement, Merck will pay $625m to Bristol and Ono, plus royalties on global sales of Keytruda.

ACCELERATED APPROVAL: "ELUSIVE AND IMPROBABLE"

Bristol's decision not to pursue accelerated approval raises questions about whether a problem emerged with data from the CheckMate 568 study. ISI Evercore analyst John Scotti said in a Jan. 19 note that the company is not planning to release data from the '568 trial for competitive reasons.

Bernstein Research analyst Tim Anderson said, also in a Jan. 19 note, that the company's most likely plan for early registration included data from the CheckMate 568 study plus data from the Phase I/II CheckMate 012 study.

"To us, BMY's early filing plans seemed elusive and improbable because: (1) '568 had no control arm (for reasons we never understood); (2) BMY would be attempting to do this on the back of its surprising and still-not-fully-explainable failure with Checkmate-026; and (3) in 1L lung cancer, there are a variety of treatment options already available (including Merck's competing PD-1, Keytruda, which was approved in Oct. 2016)," the analyst said.

Hilliard Lyons analyst Kurt Kemper wrote in a Jan. 20 note that his firm had not incorporated an early filing into its investment thesis, because of the lack of comparator arm in the CheckMate 568 study, but Lyons pointed out that the vagueness of Bristol's announcement nevertheless raises risk.

The company is likely to be pressed for further explanation of the decision during its earnings call Jan. 26.

Bristol is now expected to file the combo using data from the CheckMate 227 study, which could be in 2017 if the trial hits on interim analysis or in the first quarter of 2018 at the latest.

"Without offering timelines, BMY did confirm that interim efficacy evaluations are incorporated into all of their registrational studies – leaving some room for a surprise, but the vacuum of information around this update certainly hurts our conviction in BMY's ability to replicate the very impressive CM-012 results," Leerink Swann analyst Seamus Fernandez said in a Jan. 19 note.

A BETTER FILING PACKAGE

While the news clearly is a setback for Bristol, it could mean that the company will be in a stronger position when it gets to FDA. Unlike Merck, Bristol was filing for approval of a totally unproven drug combination. Opdivo is not approved as a monotherapy for first-line lung cancer and Yervoy is not cleared in lung cancer at all. Plus Yervoy, while very potent, can be highly toxic with side effects that need to be carefully managed.

Furthermore, with Merck's Keytruda/chemo combo under review and likely to be approved even before the May user fee date, the case would be harder to make for a Bristol accelerated approval.

William Blair analyst John Sonnier said in a Jan. 20 note said that while it was worthwhile to investigate the opportunity, the lack of a control arm in the CheckMate-012 and CheckMate-568 studies would have made an accelerated approval difficult. However, this does not change expectations for the potential of the combination in first-line NSCLC in the CheckMate-227 study, in the analyst's view.

"Bristol is now expected to file the combo using data from the CheckMate 227 study, which could be in 2017 if the trial hits on interim analysis or in the first quarter of 2018 at the latest.

Jefferies analyst Jeffrey Holford said in a Jan. 19 note that Bristol's update was in line with expectations and could reflect the evolving NSCLC landscape.

Holford commented that "Bristol-Myers management may have set a high hurdle in terms of what could drive an accelerated filing approach."

As for Merck's regulatory strategy, even though the KEYNOTE-021 study was positive, Jefferies analysts viewed Merck's surprise early filing as a high risk move due to several weaknesses in the study, as well as its prior failure to gain a compendia listing.

ASTRAZENECA ALTERS MYSTIC DESIGN

Bristol's delay is good news for other competitors besides Merck. Roche's IMpower-150 study of its PD-L1 inhibitor *Tecentriq* (atezolizumab) combined with *Avastin* (bevacizumab) and AstraZeneca PLC's MYSTIC study of its PD-L1 inhibitor durvalumab with its CTLA-4 inhibitor tremelimumab are both due to read out this year.

With CheckMate 227 due to read out in the first half of 2018, this gives AstraZeneca a potential head start with its PD-L1/CTLA-4 combination if the MYSTIC study is positive, Fernandez commented.

AstraZeneca announced Jan. 17 that it was changing the design of the MYSTIC study. Originally, the plan was to test durvalumab monotherapy and durvalumab/tremelimumab against standard of care chemotherapy, using progression-free survival as the primary endpoint. The company announced the protocol was amended, however: it will now assess PFS and overall survival in patients with PD-L1-expressing tumors for durvalumab monotherapy and the combination, as well as in all-comers (regardless of PD-L1 expression) for the combination compared to standard of care chemotherapy.

The company noted it was able to make the adjustments to the ongoing trial, because of its "flexible trial design." The changes should make for more competitive labeling in terms of PD-L1 expression, and could better support approval for durvalumab monotherapy as well.

"While the focus remains on exploring the benefit of durva + treme as combination therapy, the company has updated the endpoints of the MYSTIC trial to include OS and PFS in durvalumab monotherapy. This is based on recent internal and external data, including durvalumab's strong efficacy in monotherapy presented at recent medical meetings, as well as significant opportunities in the competitive landscape," the company explained.

AstraZeneca expects PFS data in the middle of this year and final overall survival data "at the latest in 2018." Interim analyses will also be done, but timing has not been disclosed.

The new plan appears to place more importance on durvalumab as a monotherapy, Bernstein's Anderson observed in a Jan. 20 note.

"Bulls will claim it is smart for AZN to hedge its bets with both mono- and combination therapy. Bears will claim AZN may have less confidence than before in the CTLA4 combination approach, which has been at the core of its IO development program," he said.

Analysts expect a filing of the durvalumab/tremelimumab combination in the second half of this year.

Published online January 20, 2016

US FDA Touts Value Of Phase III Trials Amid Presidential Transition

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Shutterstock: Joseph Sohm

In what could be a notice to the incoming Donald Trump administration and any reform ideas it may have, the US FDA has reiterated its long-held wisdom that randomized, controlled Phase III clinical trials (RCTs) should remain the gold standard to meet the risk/benefit threshold for approval.

A report released Jan. 19, the eve of inauguration day, notes that although advances in science have allowed for some flexibility in clinical trials – such as the use of biomarkers and surrogate endpoints – Phase III trials "help care providers understand when a medical product provides clinical benefit to patients that outweigh the risks."

The evidence mustered in the report could bolster two fundamental tenets of FDA's policies: that medical products shouldn't be marketed until thoroughly investigated, and that once on the market, new claims about products should meet a similar standard. The arguments may be needed as the policies could face challenges in the years ahead.

One challenge is long-standing and could have produced regulatory changes even if Hillary Clinton had won the White House – off-label communications, the idea that sponsors should be able to discuss the available science, not just the FDA-sanctioned language, for products once they are approved. Off-label communications has been gaining ground in the courts for years, so FDA could have found its hands tied on the issue regardless of who was president, and it is likely to find a sympathetic ear in any Republican administration, despite what the outgoing agency leadership has to say about the constitutional underpinnings of the current approach to promotional oversight.

The other issue regarding Phase III trials seems uniquely Trumpian. The new president has been weighing FDA commissioner candidates early and openly, and the two names floated publicly (Jim O'Neill and Balaji Srinivasan) are very much in the vein of some of his cabinet picks – people with substantial business and limited to no government experience who have a decidedly skeptical view of the aspect of government they would be tasked with running.

Both O'Neill and Srinivasan have expressed real skepticism about the need for FDA to vet a product's efficacy before approving it. And while the statutory language that allows the agency to do so seems unlikely to be revised anytime soon, a determined commissioner might be able to affect regulatory changes that shift its meaning in a practical sense.

Given this backdrop, FDA's data-driven argument for rigorous studies seems almost as quaint as it is strong. The agency's report showcases 22 different case studies of drugs, vaccines and medical devices demonstrating instances where promising Phase II clinical trial results were not confirmed in Phase III. (*See pie chart*)

The report comes on the heels of what the agency describes as, in recent years, "growing interest in exploring alternatives to requiring phase III testing before product approval, such as relying on different types of data and unvalidated surrogate endpoints." Despite the long-running issues, the timing of the release likely has more to do with the Presidential transition than scientific developments.

"This paper is not intended to assess why each of these unexpected results occurred or why further product development was not pursued," the report states. "Rather, these cases, chosen from a large pool of similar examples, illustrate the ways in which controlled trials of appropriate size and duration contribute to the scientific understanding of medical products."

Phase III trials "also help researchers understand when a purported mechanism of action is credible and merits further development, allowing researchers to avoid investing substantial time and resources going in the wrong direction, resources that could be deployed to identify a truly effective product," the report states. "As we continue to explore alternatives to requiring phase 3 test-

The report comes on the heels of what FDA describes as, in recent years, "growing interest in exploring alternatives to requiring Phase III testing before product approval, such as relying on different types of data and unvalidated surrogate endpoints."

Types of Divergence

Source: FDA report on where Phase II and III trials had divergent results

ing, it is important to keep in mind the benefits they provide to both patients and to the medical research enterprise."

Of the 22 trials examined, Phase III trials did not confirm Phase II findings of efficacy in 14 cases, safety in one case, and both safety and efficacy in seven cases. In some cases of Phase III – such as Pfizer Inc.'s cardiac events reduction candidate torcetrapib – patients on the product being studied in saw an increase in the frequency of the problem that the product was designed to prevent.

According to the report, patients who took torcetrapib were 25% more likely to suffer a major adverse cardiac event than those taking the placebo. Subjects taking torcetrapib also showed a significant increase in blood pressure. The safety and efficacy issues resulted in the trial being terminated three years earlier than expected. Biomarkers in Phase II development were initially promising, as torcetrapib patients showed improved cholesterol levels.

The Phase III trial for Eli Lilly & Co.'s Alzheimer's disease candidate Semagacestat was also terminated before completion, despite promising biomarker results in Phase II. Semagacestat – specifically designed for the improvement of cognitive and functional status in subjects with Alzheimer's – was shown to have reduced blood levels of amyloid-beta, which researchers hypothesized to reduce symptoms of the disease.

In Phase III, however, patients who on the drug had worsened cognitive and functional status and compared with those on placebo, and also developed an increased risk of skin cancer.

Lilly's star-crossed Alzheimer's program has also produced an example of the value of another regulatory principle that FDA holds dear: avoiding subgroup analyses that are not prespecified

CLEAR EFFICACY, BUT POOR SAFETY PROFILE

One of the drugs studied demonstrated a clear case of efficacy to an FDA advisory committee, but only obtained approval with a Risk Evaluation and Mitigation Strategy.

Lilly's *Zyprexa Relprevv* (olanzapine pamoate), a long-acting, injectable formulation of its atypical antipsychotic olanzapine for the treatment of patients with schizophrenia, previously showed non-inferiority to the oral formulation of the drug in early clinical development. was effective in reducing the severity and frequency of schizophrenia symptoms.

In Phase III development, however, there were two episodes of profound sedation observed in the first hour following injection. There were also reports of sedation, dizziness, confusion and/or loss of consciousness, with some coming in the immediate post-injection period and some as late as three hours after injection.

The advisory committee still recommended approval because "it would be worth trying to manage the risks of the injectable formulation in order to make the product available for patients with a history of non-adherence," the report states. FDA later approved the drug with a REMS.

SEVERAL VACCINES SAFE, BUT NOT EFFECTIVE

Of the 22 products studied, 14 were found to not be efficacious in Phase III clinical trials, four of which were vaccines. (*See table p. 18*)

One was a genital herpes vaccine developed by Chiron, which is now Novartis Vaccines & Diagnostics Inc. In Phase II development, subjects who received the vaccine showed an antibody response similar to those who had a naturally-acquired HSV-2 infection. The promising results faded in Phase III though when vaccine recipients acquired HSV-2 infection at a rate similar to those in the placebo arm.

Another example was GlaxoSmithKline PLC's MAGE-A3 vaccine for the treatment of patients with non-small cell lung cancer (NSCLC) following surgery. Although there was a small improvement in disease-free survival and overall survival among patients receiving the vaccine in a proof of concept trial, the vaccine showed a statistically non-significant improvement in disease-free survival in Phase III.

Published online January 22, 2016

Phase III Floundering: Products That Didn't Live Up To Early Results

PRODUCT NAME	PRODUCT TYPE	TREATMENT AREA	SPONSOR	TYPE OF DIVERGENCE
Bitopertin	Drug	Schizophrenia	Roche	Efficacy
Brivanib	Drug	Hepatocellular cancer	Bristol-Myers Squibb	Efficacy
Capsaicin Topical Patch (Qutenza)	Combination product	HIV-associated nerve pain	NeurogesX	Efficacy
Darapladib	Drug	Prevention of cardiovascular disease complications	GSK	Efficacy
Dexmecamylamine	Drug	Depression	Targacept/AstraZeneca	Efficacy
Exhale Drug-Eluting Stent	Device	Reduction of shortness of breath in patients with emphysema	Broncus Technologies	Efficacy
Experimental HSV-2 Vaccine	Vaccine	Prevention of genital herpes	Chiron	Efficacy
Glutamic Acid Decarboxylase Vaccine	Vaccine	Preservation of insulin secretion for patients with recent-onset type 1 diabetes	Diamyd Medical	Efficacy
Imiquimod (Aldara 5% Cream)	Drug	Molluscum contagiosum lesions	3M	Efficacy
Iniparib	Drug	"Triple negative" breast cancers	Sanofi	Efficacy
Lithium	Drug	Amyotrophic lateral sclerosis	King's College London	Efficacy
MAGE-A3 vaccine	Vaccine	NSCLC	GSK	Efficacy
NicVAX vaccine	Vaccine	Smoking cessation	Nabi Biopharmaceuticals	Efficacy
Velimogene Aliplasmid (Allovectin-7)	Drug	Metastatic melanoma	Vical	Efficacy
Zyprexa Relprevv (Olanzapine Pamoate)	Drug	Schizophrenia	Lilly	Safety
Tekturna (Aliskiren)	Drug	Prevention of congestive heart failure complications	Novartis	Safety and Efficacy
CoStar Drug-Eluting Stent	Device	Reduction of heart attack risk	Conor Medsystems	Safety and Efficacy
Figitumumab	Drug	NSCLC	Pfizer	Safety and Efficacy
Recombinant Factor VIIa (NovoSeven)	Drug	Reduction of intracerebral bleeding and hematoma size	Novo Nordisk	Safety and Efficacy
Semagacestat	Drug	Improvement of cognitive and functional status in subjects with Alzheimer's Disease	Lilly	Safety and Efficacy
Torcetrapib	Drug	Prevention of cardiovascular events	Pfizer	Safety and Efficacy
V710 vaccine	Vaccine	Prevention of Staphylococcus aureus infection	Intercell/Merck	Safety and Efficacy

Industry Wants Fixes To EMA's Guidance on Clinical Data Publication

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Drug companies are calling on the European Medicines Agency to employ a more structured approach to its continuous revision of its guidance document on implementing Europe's landmark policy on proactively publishing clinical data. In addition, industry is worried about one of the first set of revisions the agency made to the guidance in December 2016 that it fears will be a challenge for companies and is exploring alternative solutions.

The guidance is a "living document." The EMA first published it on March 3, 2016 and is revising it as it gains more experience with implementing the policy and processing submissions from companies whose clinical reports are being published. The policy, which entered into force in January 2015 and went live with the publication of the first clinical reports in October 2016, is the first of its kind and is proving to be a learning curve for both the EMA and industry.

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> EMA will hold quarterly webinars on future revisions to the guidance. Industry raised concerns about learning about revisions early enough – not after they had already nearly finished working on their submissions.

EMA PROMISES QUARTERLY UPDATES

The EMA announced the first revisions to the guidance during a webinar on Dec. 9, 2016, that the agency held to give companies an update on how it was faring with the clinical data publication initiative – which is also known as Policy 0070.

The agency also agreed to start scheduling quarterly webinars to keep industry abreast of future revisions to the guidance, after webinar participants from industry raised concerns over whether they would learn of the revisions early enough – not after they had already nearly finished working on their submissions. Moreover, the EMA encouraged companies to get in contact with the agency even before a quarterly webinar was due to discuss on an ad hoc basis any solutions for implementing the policy that they might have identified.

Nevertheless, the European drug industry federation EFPIA has concerns about the revisions and how they are being made. It told the Pink Sheet that while it welcomed "the continuous dialogue with the EMA in implementing the policy" and looked forward to participating in the quarterly webinars, it still wanted to see "more structure in the way changes are introduced" in the guidance document.

THE PROBLEM WITH REMOVING PAGES

The guidance document explains how a company should go about the arduous task of preparing and submitting the redaction proposal document package that is required under the policy to anonymize individuals who took part in the trial and remove any commercially confidential information (CCI) before a clinical report can be published.

Following the revisions, EFPIA believes "a few specific technical solutions still need some consideration" and that they "should be left for the sponsor to determine at this stage." These technical solutions, the trade group clarified, are needed to achieve the desired end result of the clinical data publication policy – i.e., the utility of the data being disclosed, while ensuring protection for the participants in the trial.

For example, one revision that might pose problems for industry, EFPIA said, concerns new instructions to remove (and not redact) pages in the clinical report relating to certain individual patient data (IPD) that is deemed to be "out of scope" of the policy and replace them with white (or blank) pages containing text to indicate which page numbers and sections were removed and why.

Removing pages from the clinical report is designed to fulfil the visual requirement

set out in the policy for transparency in the way that possible redactions are being made, EFPIA explained. But doing so would create challenges for companies, it warned.

As a spokesperson from the European Confederation of Pharmaceutical Entrepreneurs (Eucope) explained during the webinar, even though replacing pages in a report with blank ones might sounds like a minor task, it would entail companies having to republish their entire document.

Anonymizing reports for the policy is a new concept that is still being developed and the EMA is planning to establish a technical advisory group on anonymization.

EFPIA noted that industry associations had been requested during the webinar to propose an "acceptable and technically feasible approach that would fulfil the visual requirement as well." It said it was "liaising with its members, and other trade associations, on alternative proposals since there are several techniques that may be used by companies to achieve the objective."

The EMA's Deputy Executive Director Noël Wathion warned, however, that he did not want to see proposals that involved "pages and pages" of redacted text. This would not be in the interest of transparency. It would "create a perception that frankly speaking we can do without," he told the webinar participants.

A POSITIVE ATMOSPHERE OF COLLABORATION

Policy 0070 entered into force on Jan. 1, 2015 and applies to clinical data that are submitted by drug companies to support their regulatory applications for human medicines under the centralized procedure. The EMA is publishing the data for the applications concerned since the policy entered into force, chronologically according to the date of the opinion of the EMA's drug evaluation committee, the CHMP. Clinical reports have been published for six products so far (the first two were published on Oct. 20) and, as of Dec. 9, 2016, there was a backlog of around 100 procedures that the agency has been working on.

"There are several areas where we will learn from the experience, and where further dialogue is needed to ensure efficient ways of working," EFPIA said.

The EMA also recognizes that there is much to iron out. "Each time when you start [a procedure] with a new company it is on a new learning curve, certainly for the company concerned but also for ourselves," Wathion said. "We identify issues each time that we have not yet covered, so the guidance… will remain a living document for the next months to come."

"It's been quite intense and very challenging," Wathion said of the EMA's experience with policy so far. Nevertheless, "we would like to thank all the companies with whom we have had the pleasure to interact," he declared". "Everything was done in a very positive atmosphere of collaboration."

GETTING ANONYMIZATION RIGHT

Anonymizing reports for the policy is a new concept that is still being developed and the EMA is planning to establish a technical advisory group on anonymization.

"We are all on a learning curve" with anonymization," said Anne Sophie Henry-Eude, Head of Document Access and Publication at the EMA.

For example, "there is not always a common understanding about what we are speaking about with IPD," Henry-Eude told the webinar participants. "For some it's the data set, for some people it's the raw data, for some people these are the line listings. We wanted to try as much as possible to define IPD in the context of the policy."

The EMA expects to create the new group on anonymization early this year. "We will probably launch a public call for expression of interest to experts to be part of the group and those experts can come from academia, patient organizations and the pharmaceutical industry," Wathion said. "We would like to see how can we on the basis of the current guidance further develop this all together because at the end of the day we are all in the same boat," he said, reflecting on the policy's aim to increase the utility of the information that is published.

In the meantime, when dealing with anonymization, Henry-Eude advised companies to follow the template provided and ensure things are very clearly written and are adapted to the products and the type of studies. She added that:

- identifiers should be clearly listed;
- data utility must be considered;
- report must match the proposed redactions; and
- labeling of redaction must be followed.

EXTENDING THE SCOPE OF THE GUIDANCE

Among the other revisions to the clinical data publication guidance, the agency has extended the scope of Policy 0070 so that all clinical reports that are submitted as part of, or cross-referred to within a regulatory application in the context of the policy are subject to publication. This includes clinical study reports that have been previously submitted in the context of earlier regulatory procedures that form the basis of the regulatory decision for those applications falling within the scope of Policy 0070.

Another revision deals with marketing authorization transfers. Where an applicant/marketing authorization holder (the transferor) transfers a marketing authorization to another company (the transferee), the transferee becomes responsible for the transferred product and accepts all prior agreements under policy 0070 between the transferor and the EMA, the updated guidance says. If the policy 0070 process has already started with the transferor, the process will continue as normal with the transferee taking over from the transfer date.

A summary of the all revisions is available on the EMA's website.

From the editors of Scrip Regulatory Affairs. Published online January 20, 2016

J&J Promotes Preventive Care, Wellness In US Health Debate

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On the heels of his meeting with President Trump, Johnson & Johnson CEO Alex Gorsky utilized the company's year-end earnings call to lay out the firm's legislative and business advocacy priorities, which include supporting policies toward preventive care and wellness, topics of particular interest to the consumer products segment.

The discussion occurred just two days prior to the firm's announcement of its deal with Switzerland-based rare disease company Actelion Ltd., for $30bn, which does not involve the consumer unit that includes OTC pain relievers under the *Tylenol* and *Motrin* brands, allergy medicines *Benadryl* and *Zyrtec*, and mouthwash *Listerine*.

Many of the headlines coming out theJan. 24 earnings call centered on prescription drug pricing transparency and J&J's call for US tax reform to encourage innovation and growth.

But OTC drug makers could get a boon from changes to the Affordable Care Act, if they eliminate a current ACA provision requiring consumers to receive prescriptions for OTC drugs in order to pay for the products with pre-tax savings accounts. Removal of that provision is one of the Consumer Healthcare Products Association's priorities.

Gorsky did not address that issue directly. He did say the company will advocate that any replacement of the Affordable Care Act – P.L. 111-148 – include measures for increased health care access and to retain the Act's language mandating that insurers cover pre-existing conditions and that young adults can continue to be covered under their parents' coverage, he said.

More broadly, though, Gorsky shed light on efforts to push forward policies promoting preventive care and wellness initiatives in the workplace.

"We support reforms that emphasize wellness in intercepting disease before it happens," Gorsky said. "Preventive care, more latitude for employer wellness programs and incentives for healthy behaviors are great ways to embody this focus," he said.

OTC drug and dietary supplement firms have for years touted the role their products could play in supporting reduced doctor's visits and Rx drug consumption in the US. This includes encouraging consumers to take dietary supplements to maintain wellness, and turning to OTC drugs to address minor health ailments that otherwise would require a doctor's visit.

Recently, members of a National Institutes of Health advisory committee discussed the prospect of expanding insurance for natural health products and complementary health care services to reduce consumers' use of pharmaceutical pain treatments.

CONSUMER HEALTH SALES UP ON ANALGESICS

J&J reported that its overall consumer segment sales – which represent 19% of group sales and include OTC drugs, baby care, beauty care, women's care and oral care – climbed 3.4% in the fourth quarter on a reported basis to reach $3.43bn (figures issued before the Actelion deal). "Despite global consumer category slowdown, we did continue to see strong consumption for many of our products," said J&J VP Investor Relations Joseph Wolk, noting a marked 17.7% growth for the beauty segment to $1.06bn reflected newly acquired brands.

Johnson & Johnson CEO Alex Gorsky

> OTC drug makers could get a boon from changes to the Affordable Care Act, if they eliminate a current ACA provision requiring consumers to receive prescriptions for OTC drugs in order to pay for the products with pre-tax savings accounts.

The OTC sub-division of consumer health grew 2.1% to $1.04bn, the firm reported. The Zyrtec allergy brand continued to gain market share and J&J's total adult analgesic products (which include Tylenol and Motrin) were up one share point to 14.3%, while pediatric analgesics gained four share points from the fourth quarter of 2015 with a share of 49.8%.

The share gains stemmed from a bounce following lower inventory levels in the last quarter that impacted growth, Wolk said. "In the fourth quarter, we did see a replenishment of that inventory to match the higher demand as well as some seasonal build." That led to an 8.3% increase in reported growth to $418m for US OTC products in the fourth quarter.

The exec commended the J&J team for the remediation of the analgesics business following a massive recall in 2011 of the firm's OTC drugs including Tylenol and Motrin after FDA discovered quality control issues in its manufacturing facilities. The company operated under a consent decree with the agency and has since remediated all three of its manufacturing sites and returned products to store shelves.

"I think the team has done really a remarkable job of meeting all the FDA requirements," Wolk said. "And by the way, we did that while reinvesting right here in Pennsylvania in the United States at a plant in Fort Washington that we now feel is world-class and really will set the standard around OTC production going forward."

The US portion of consumer health sales advanced 12.7% to $1.39bn and the international sector slipped 2.1% in the quarter to $2.05bn.

For the year, J&J's consumer segment sales fell 1.5% to $13.3bn. Sales for the US portion for the year grew 3.8% to $5.42bn and international sales dipped 4.8% to $7.89bn, the company reported.

J&J's net sales for the year, which also include the pharmaceutical business, advanced 1.7% to $18.1bn in the fourth quarter and full year sales grew 2.6% to $71.9bn. A strong performance of J&J's pharmaceutical business helped boost reported net earnings in the quarter to $3.8bn, representing growth of 18.6%. For the year, earnings reached $16.5bn, an increase of 7.3%.

From the editors of the Tan Sheet. Published online January 25, 2016

China FDA Video Showcasing 'Hard Work' Grips Social Media

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The video has generated so much interest that one embedded article recorded more than 25,000 views shortly after posting.

The hope for new drugs to gain quicker approvals in China has never been higher. But expectations may have to be tempered somewhat given a number of ongoing challenges, suggests the country's main drugs regulator, the China FDA, in a new video that has been gaining wide social media attention.

Outside the China pharma regulatory affairs cycle, few people can imagine how hard the agency has been working towards this goal, the CFDA declared, explaining that this is why it had decided to make the video to explain and showcase its efforts.

The video, released on Jan. 11 just days before the start of the Chinese New Year at the end of this month, has generated so much interest that one embedded article recorded more than 25,000 views over the following weekend.

'STRETCHED THIN'

In the video, the CFDA explained that its main approval review body, the Center for Drug Evaluation (CDE), is being stretched thin by its high workload, which could pose hurdles to several recent initiatives by the agency to accelerate investigational new drug approvals in the world's second-largest pharma market.

Highlights Of New Drugs Under CFDA Review

NAME	SPONSOR	INDICATION	REVIEW STARTING TIME
KY0467	Kanion Pharma	Breast cancer	Dec.1, 2016
Benzenediol	Guangdong Zhonghao Pharma	Psoriasis	Dec.9, 2016
APG-1252	Ascentage Pharma	Small-cell lung cancer	Dec.30, 2016

Source: CDE, DXY PharmaInsight

Besides the usual mountain of paperwork associated with these and new drug application filings, drug reviewers working at the CFDA also face external pressures, the agency said, stressing that the CDE has indeed been working hard to eliminate the "drug lag".

For one, a shortage of reviewers has been a chronic issue facing the center. With over 7,000 drug review cases annually, many reviewers already regularly work overtime and the agency has had to resort to borrowing additional hands from provincial FDAs, who have even given up their holidays and time off.

Meanwhile, many reviewers have chosen to leave their grueling jobs at the CFDA and take higher-paying positions elsewhere, creating an even bigger hole to fill, acknowledged the regulatory agency.

Not only multinational drug makers but also domestic heavyweights including Fosun International Ltd. and Jiangsu Hengrui Medicine Co. Ltd. are luring regulatory professionals away with larger pay packets and easier work conditions.

HELP WITH GUIDELINES

As part of a new effort to involve the pharma industry in its activities, the CFDA is soliciting comments on how to improve its guideline setting and editing process. The agency plans to organize a discussion forum attended by industry associations, universities, research organizations, and CROs on Jan.18.

WATCH

Visit http://bit.ly/2jjTkdN to watch the CFDA video in Chinese.

The regulatory body is also recruiting representatives from 10 drug companies to attend the meeting, with a goal of getting the pharma industry more involved in regulatory affairs and to accelerate the setting and modification of guidelines.

One of the tasks for the agency is to increase the transfer of international R&D and technical guidance, it said.

DOUBTS REMAIN

Two years ago, China made a promise to eliminate a drug approval backlog of over 10,000 filings, and to begin a rolling review process starting in 2018. But with less than a year to go to that date, the agency – with the help of the new video – is now urging patience.

The video effectively served as a pat on the back for drug reviewers, calling them "unsung heroes", meanwhile serving to seek understanding from applicants who may be wondering what's going on with applications that were filed long ago.

"The agency is trying to let the public understand the challenges, and reassure the industry, 'tomorrow will be better'," the former international business manager of Shanghai-listed domestic drug maker Yabao Pharmaceutical Co. Inc., Luo Shizhong, told Pink Sheet.

Others disagree. One reader left a comment at the end of the article asking, "If they have the time to make the video, why can't they devote more efforts to focusing on their work?"

"We need no slogans nor videos, nor repeated words or talking during Q&As at each of your training sessions, but your solutions to real problems. I hope experts [sitting on review committees] can take their responsibilities and work hard."

STATIC NUMBERS, NEW DRUGS

Although the agency is stepping up efforts to shed more light on its activities, even going as far as the video, the number of product cases and approvals it is tackling remains largely the same.

In December, for instance, the CDE accepted a total 256 applications for chemical drugs and biologics as well as traditional Chinese medicines, both domestic and imported products, compared to 253 in November, 209 in October and 261 in September last year.

Among these, 208 were chemical drugs and 20 new drugs (Category 1.1). The products included KY0467, an EFGR/HER2 TKI inhibitor from Jiangsu Kanion Pharmaceutical Co. Ltd., and APG-1252, a Bcl-2 class anticancer agent from Ascentage Pharma Group Corp. Ltd. (*see table*).

Class 1.1 new drugs with large clinical needs, such as anticancer and HIV/AIDS treatments, usually get CFDA prioritization for faster reviews.

Also in December, the CDE took on 18 imported drugs for review, including 10 Class.5 drugs, meaning they had been marketed outside China and thus are not considered to be new drugs.

One of the imported new drugs for which an NDA has been filed first in China is peficitinb (ASP015K), a Janus kinase (JAK) inhibitor from Astellas Pharma Inc. for rheumatoid arthritis.

From the editors of PharmAsia News.
Published online January 20, 2016

New Network To Boost Coordination On Innovative Drugs Across Europe

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A voluntary initiative being supported by the European Medicines Agency and the Heads of Medicines Agencies to help all EU member states coordinate with each other when it comes to identifying and supporting the development of innovative medicinal products at national level has got off to a start.

The EU Innovation Network (EU-IN) was formalized as a new working group last year to enable better coordination between the national-level innovation offices of various member states, as well as the EU member states that have not yet established such offices but still want to support innovative medicines.

The setting up of national-level innovation offices has gathered momentum over the last decade. Most recently, Belgium announced plans to establish a national innovation office, while Ireland opened one last year. Both Belgium and Ireland are now members of the EU-IN, which currently has 17 members, including the EMA that provides the secretariat for the innovation network.

The network is co-chaired by Esa Heinonen, director of medicines evaluation at the Finnish Medicines Agency, and Marisa Papaluca-Amati, senior scientific adviser at the EMA's Division of Scientific Committees Regulatory Science Strategy. The aim is to add more members to the EU-IN in 2017, said Papaluca-Amati told the Pink Sheet.

Papaluca-Amati explained that the EU-IN will allow participating member states to not only keep abreast of the types of innovative medicines being developed in each other's countries, but also to leverage the expertise in the network to support the development of innovative products nationally.

For example, she explained, if Finland (which is also an EU-IN member) were to come across a very innovative advanced therapy medicinal product (ATMP) that posed a regulatory challenge because of the nature of the treatment, then the Finnish authority could discuss this product or other identified bottlenecks impeding the development of the product in the innovation network.

It would allow the Finnish agency to see if similar products are being developed elsewhere and what approach was taken to support their further development. "So the members of the [innovation] network can communicate among themselves… [and] leverage European knowledge. This is extremely important at the local level," Papaluca-Amati said.

The EU-IN is open to all member states irrespective of whether or not they have set up a national-level innovation office, clarified EMA's scientific officer, Falk Ehmann, who is responsible for the management of the agency's Innovation Task Force. In order to join the EU-IN, the member state only needs to identify an "innovation contact", whose duty would be to ensure that there is seamless flow of information between the concerned national authority and the EU-IN.

For its part, the EMA's Innovation Task Force is sharing information about its work with the agency's human medicines evaluation committee (CHMP), "where representatives from each member state are present and they are invited – or I should say encouraged – to join our cause because the intention is to grow," Ehmann said.

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The EU-IN was officially established in October last year, when it held its inaugural meeting and a formal mandate was adopted. Thereafter, EU-IN members met on Jan. 12, 2017 to begin work on implementing the mandate under a new co-chair. This year, the network will focus its efforts on consolidating its working methods, sharing best practices and encouraging more member states to join in.

CAPITALIZING ON DIFFERENCES

The EMA established its Innovation Task Force in 2001. Between 2009 and 2011, certain member states –such as the UK, Sweden and Germany – started setting up their own national-level innovation offices.

The main focus of national innovation offices has been to provide a platform for innovators (mostly academic spin offs, small enterprises, etc), who are looking for early support for their innovative medicinal products or for new methods for innovation in medicines development.

In 2011, the EMA thought that everyone should try and work together "because you can amplify your knowledge-building if you see innovations coming in from different constituencies," Papaluca-Amati said. This resulted in the EMA's Innovation Task Force holding informal teleconferences with national innovation offices on a routine basis.

"What happened is that… [gradually] we realized that a lot of innovation occurring in Europe was not visible to all [national] innovation offices [and some national-level] offices themselves were not visible enough to the innovators… [Also, it became apparent that these innovative products were] not visible to the entire system. So the preparedness of the entire European [medicines] system to bring those innovations to patients needed to be further reinforced," Papaluca-Amati said of why the EU-IN was created.

As more national-level innovation offices are still being rolled out, the EU-IN does not intend to offer any specific guidance on how these should be shaped. Far from ensuring that all national

offices should look and do the same work, Papaluca-Amati said "we want to capitalize on our differences".

At present, the EU-IN is looking at every national innovation office and "innovation contact" (in member states without national-level offices) and is mapping out exactly what kind of innovations they each see and support, what kind of processes they have in place and what kind of innovators they meet - for example, is it more SMEs, academia, consortia or consultants.

By the end of March, the EU-IN hopes to develop a core profile that is common to all innovation offices and also identify areas that are of particular interest for each office. "So there may be innovation offices, for example, that do not deal with certain types of innovative products, but they will have a list of colleagues who specialize in such products and therefore they can leverage the common knowledge," she added.

> EU-IN will make publicly available a list of "contact points" in each national innovation office so that innovators know to whom they should write if they want to put a question or query to their local national authority.

Also by the end of March, the EU-IN will make publicly available a list of "contact points" in each national innovation office so that innovators know to whom they should write if they want to put a question or query to their local national authority.

While the EMA already gets a good deal of exposure to very novel, breakthrough innovative products, Papaluca-Amati said: "We see only a fraction of what is going in Europe and the worry is about those [innovators] who will never approach the agencies". The EU-IN will ensure that innovators are aware of innovation contact points in each EU member state, where can they get support and advice about their products. "It's about increasing visibility of what the national competent regulatory authorities are prepared to offer to innovators in Europe," she added.

In addition, it is important for the network to understand what regulatory scientists regard as challenges and opportunities for the regulatory system, especially when they identify "disruptive innovation", which requires the regulators' attention. This will help the network to be prepared.

The EU-IN is also expected to help with matters that serve the purpose of keeping the EU regulatory system fit for purpose vis a vis of innovation, such as horizon scanning, identifying training needs, contributions to prioritization, etc.

THE IRISH INNOVATION OFFICE

The Irish Health Products Regulatory Authority launched its national innovation office in November last year. As of Jan. 6, it had received and addressed nine queries in relation to various types of innovations, including medicinal products, medical devices, combination products and diagnostics that are currently under development and manufacturing and testing technologies, an HPRA spokesperson told the *Pink Sheet*.

The office acts as an "initial point of contact" for any queries relating to innovative products and offers free regulatory advice and assistance in relation to novel products. Queries can be submitted in relation to initial research and design, formulation, testing, clinical studies or manufacture. The aim is to help ensure that innovators have a clear understanding of the regulatory pathway that applies to a new product, and that they avoid, where possible, regulatory issues which could potentially occur at various stages of the development process.

In addition, the Irish regulator has established a "horizon scanning group", which is tasked with regularly reviewing information gathered through a wide range of sources (including queries to the innovation office) about innovations or developments of interest to the HPRA.

These initiatives, it explained, are being launched to support HPRA's Strategic plan published in 2016 to support innovation through a number of complementary activities. Other initiatives on this front include establishing a Quality, Scientific Affairs and Communications department and developing outreach programmes to optimize the HPRA's interaction with stakeholders.

Law firm Arthur Cox said it remains to be seen how the new innovation office will provide added value to the current regulatory support services made available by the HPRA, which applies to both innovative and non-innovative products alike.

From the editors of Scrip Regulatory Affairs. Published online January 22, 2016

Part D Donut Hole Provisions May Not Be Best Way To Ensure Access, Price Says

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The Affordable Care Act provisions that effectively close the Medicare Part D donut hole by 2020 are not necessarily the best way to ensure seniors have continuous access to their prescription drugs, HHS Secretary-nominee Rep. Tom Price, R-Ga., told the Senate Finance Committee at his confirmation hearing Jan. 24.

In response to a question from Sen. Bill Nelson, D-Fla., Price declined to promise that he will work to retain the current donut hole provisions if the Affordable Care Act is repealed.

The ACA sets out to close the Part D donut hole in two ways. First, it has required manufacturers to provide 50% discounts on the cost of branded drugs while seniors are in the donut hole since 2011. And second, the law began requiring Medicare plans to assume increasing responsibility for covering the cost of drugs in 2013 with the aim of effectively closing the donut hole in 2020.

Nelson was referring to both the manufacturer discounts and the gradually increasing coverage in his question to Price, a spokesman said. For manufacturers, the discounts have been a financial burden but at the same time, they have encouraged beneficiaries to stay on a brand and not switch to a lower cost drug while in the donut hole.

"I think it's imperative that we provide the greatest opportunity for individual seniors to gain access to the drugs they need," Price answered. But "so often in these discussions we think that whatever we're doing now is the only solution possible and I'm humble enough to believe that there are better ideas out there.

"If we find a better idea that actually provides greater coverage at a lower cost more efficiently and more responsive to patients, we ought to be able to admit to ourselves that we would embrace that if it came along."

"I can't get away with an answer like that," Nelson responded. "I have to tell [my constituents] that 'I'm going to support your right to get drugs under Medicare Part D just like you're getting them now and not take it away from you.'"

So "often in these discussions we think that whatever we're doing now is the only solution possible and I'm humble enough to believe that there are better ideas out there."

"I understand that and I would respectfully suggest if we use, as a society, the line 'we're going to maintain the kind of quality coverage we have right now unless we can improve it,' and then we just might be able to do that for you," Price suggested.

"If I gave them that answer I'd get run out of a room of senior citizens," Nelson shot back.

PAYMENT SUNSHINE, VACCINES AND HHS PRICE NEGOTIATION

Price was also vague in answering Sen. Chuck Grassley's request that he support continued implementation of the physician payment sunshine law. Grassley noted that Republicans recently unsuccessfully tried to weaken the law with proposed amendments to the Cures bill.

Under the Centers for Medicare and Medicaid Services open payments program established by the law, medical products manufacturers reported $7.52bn in payments and ownership ad investment interest to physicians and teaching hospitals in 2015.

"I hope I could get your commitment that you will enforce this act the way it was intended…Would you work with me to ensure this transparency initiative is not weakened?" Grassley asked.

"I look forward to working with you," Price said. "I believe transparency in this area and so many others is vital not just in outcomes and pricing but in so many areas, so that patients can understand what's going on in the health care system."

Grassley also questioned Price on his position on vaccines, alluding to reports that President Trump is considering establishing an expert panel chaired by vaccine skeptic Robert Kennedy, Jr. to investigate a possible link between childhood vaccines and autism. "Science and health care have identified a very important of aspect of public health, and that is the role of vaccinations," Price said.

Grassley did not ask about Medicaid rebate classifications

The issue of whether Price would support a plan to authorize direct HHS drug price negotiation in Medicare was raised by Ranking Member Ron Wyden, Ore., and in response, Price gave the same evasive answer that he gave to the Senate Health, Education, Labor and Pensions Committee during a courtesy hearing Jan. 18.

Price's position on HHS drug price negotiation, which he has long opposed, is

Shutterstock: Paul Velgos

complicated by President Trump's repeated threats to authorize a government-run bidding system to help reduce drug pricing.

"We're committed making certain that drug prices are able to be afforded by individuals so they can have access to high quality care," Price said. He noted that pharmacy benefit managers currently negotiate prices on behalf of individual plans in Part D, but added: "I think it's important to have the conversation and look at whether or not there is a better way to do that. If there is, I am certainly open to looking at it."

During the contentious, nearly four-hour long hearing, Democrats focused mainly on questions about Price's stock transactions and probing Price's assurances that any ACA repeal plan that emerges from Congress and the administration will ensure that Americans have access to affordable, quality insurance. Senators also challenged the ideas that Medicaid be transformed into a block grant program and that Congress should privatize Medicare.

The Finance Committee will send additional questions to Price in writing before scheduling a vote on his nomination. A date for the vote has not yet been announced.

HATCH DECRIES 'LIBERAL CLAPTRAP'

In closing comments, Wyden summarized Democrats' frustration with Price's responses to many of the questions. "Several hours ago I asked you, with respect to [Trump's recent] executive order on the ACA, 'will you commit that no one will be worse off,' and you ducked it. I asked, 'will you guarantee that no one will lose coverage' and you ducked that. I asked you, 'will there be a replacement [to the ACA] before all of this that would hurt working families would go into effect' and that was ducked as well."

On the other hand, Hatch was warmly supportive of Price's nomination and sharply critical of the way Democrats approached the prospect of changes to the ACA.

"If we keep going the way we're going there won't be any health care for anybody. We won't be able to afford it. … It's gradually eating up the whole doggone federal budget!" Hatch exclaimed.

To Price, he said: "to be treated like if you don't agree with some concepts that some of my colleagues do like there's something wrong with you is just beyond the pale. You not only have a great deal of experience in medicine but you've been a great congressman and you've been assigned trying to get things under control around here and you've found that it's almost impossible because we have all these people saying, 'we've got to do everything in the world' in providing health care.

"We've got to find some way of delivering all these health care benefits to people without totally ruining the country so nobody gets any health care benefits, which is where we're headed," Hatch continued. "I don't know how in the world we can continue to buy off on this liberal claptrap that you don't have to pay the piper. What you've said is we're going to try within this … system to make it work and to cover everybody, to help people whether they be poor or rich. I don't know if you can say much more than that."

Published online January 24, 2016

A Burning FDA Hiring Freeze Question: What About User Fee-Supported Staff?

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President Donald Trump's mandated hiring freeze for the US government, while simple on its face, could prove much more complicated in its application to FDA, meaning more confusion and uncertainty for agency officials.

Trump issued an executive order telling all federal executive agency heads to stop hiring new workers or filing existing positions vacant as of noon Jan. 22, excepted in limited circumstances. No new positions may be created until further notice, while the administration assesses whether it is hiring smartly and efficiently.

The order states that the freeze does not apply to military personnel, and department and agency heads have discretionary authority to continue hiring if it is for national security and public safety reasons. It also gives the Office of Personnel Management (OPM) authority to allow new hires where "otherwise necessary."

However, it is unclear how it will affect FDA. OPM and the Office of Management and Budget (OMB) likely will have to issue an interpretation for some specific cases, such as positions supported by industry user fees.

It could be days or weeks before the decision is rendered and stakeholders already are nervous.

The Biotechnology Innovation Organization said in a statement that it hopes "there will be recognition that the source of funds to pay for the FDA personnel who review and approve new drug applications, and those who support such review activities, is user fees paid for by drug and biologics developers."

"We will work with the administration and Congress to ensure that hiring commitments under PDUFA, critical to FDA's ability to carry out its public health mission on behalf of patients, is not hindered," BIO said.

The prescription drug, generic drug and biosimilar user fee renewal commitments were completed in 2016. They recently were sent to Congress for passage. But there have been questions about whether the Trump administration could decide to reopen the agreements.

Nancy Myers, president of Catalyst Healthcare Consulting, said in an interview that there is no precedent for user fee positions as they relate to a hiring freeze. She said there will be a lot of questions about the effect on the current full-time equivalents.

Myers also has said that FDA has a strong argument for an exemption from the hiring freeze because of its public health role as well as user fee investments.

John DiLoreto, executive director of the Society of Chemical Manufacturers and Affiliates' Bulk Pharmaceuticals Task Force, who helped negotiate the generic drug user fee reauthorization, said in an email that industry could end up in a situation similar to the last government shutdown, where it must pay to help support FDA operations, but that money cannot be used.

"The only difference here is that instead of being able to spend user fee funds for reviews and inspection, FDA may not be able to spend the money on new hires, which are badly needed and could force FDA to miss its goals," he said.

Since industry payments funded them and not Treasury dollars, user fee-supported employees continued to work during the government shutdown.

FDA added more than 1,200 new employees during GDUFA I, and continued adding people last year in part to help reduce the number of ANDAs under review.

HOW DOES EXISTING LAW AFFECT FREEZE?

Jeff Allen, President and CEO of the Friends of Cancer Research, said the freeze also "could potentially affect the hiring of new scientists" under the upcoming user fee bill and 21st Century Cures legislation passed last year during a Jan. 24 speech at the California Separation Science Society's annual symposium on regulatory and analytical sciences for biotechnology health products in Washington D.C.

Cures included provisions intended to help FDA hire the necessary expertise it needs. Not only was the hiring process streamlined in some cases, but FDA also was authorized to pay higher salaries, if necessary.

There is one provision in the order that could allow FDA to continue hiring in some instances. The order states that "it does not limit the hiring of personnel where such a limit would conflict with applicable law." Since the user fee programs and Cures are enacted law, FDA may be able to argue that hiring specific to them could continue.

FDA also would not be allowed to use contractors to pick up the slack. The order states that attempts to circumvent its intent by contracting outside the government will not be allowed.

HOW LONG WILL FREEZE LAST?

The length of the freeze also remains subject to interpretation, at least somewhat.

The order does not appear to be open-ended. It states that the director of OMB in consultation with the director of OPM will recommend a long-term plan to reduce the federal government's workforce through attrition within 90 days. Once the plan is put into effect the order will expire.

Steven Grossman, deputy executive director of the Alliance for a Stronger FDA, said he is unsure how the order will play out because it hasn't been interpreted by OPM and OBM yet.

"We don't know if this thing is going to last 30 days, 60 days, is it permanent?" Grossman said. "There are really just a dozen different ways this could be sliced and until we have some clarification … it's hard to know whether there's a problem or not."

Grossman also notes that even if it is interpreted in the strictest sense, there still may be opportunities to evolve that interpretation in the future.

FDA referred questions about hiring, the current number of openings at FDA and the number of positions that could be affected by the order to the White House. A White House statement on the order said it is intended "to counter the dramatic expansion of the federal workforce in recent years and the costs attendant to that expansion."

FDA's troubles hiring staff are well-documented. The agency has hundreds of openings that it cannot fill, in part because salaries are not competitive.

Among the provisions of PDUFA VI is one for the Center for Drug Evaluation and Research are recruiting improvements.

SERVICE CUTS ON THE HORIZON?

The Pharmaceutical Research and Manufacturers of America said in an email that "a stable and sustainable workforce is crucial to [FDA's] ability to keep pace with scientific advances in biopharmaceutical drug development while ensuring safe and effective medicines reach patients in a timely manner."

The National Treasury Employees Union, which represents FDA staff, said in a statement that the freeze is harmful and counterproductive. Union President Tony Reardon said backlogs will increase and service quality will decrease.

"Arbitrary cuts will leave agencies scrambling to serve the public," he said in the statement. "A hiring freeze takes away the agencies' ability to make strategic decisions about their workforce."

"Attrition is already taking a heavy toll at many federal agencies as employees depart and there is no replacement to take on the work," Reardon added. "Freezing federal hiring could lead to disastrous short-term and long-term impacts and the American people will suffer. Many of our agencies are already experiencing severe staffing shortages as a result of budget cuts and sequestration."

Published online January 24, 2016

FDA's ANDA Approvals

SPONSOR	ACTIVE INGREDIENT	DOSAGE; FORMULATION	APPROVAL DATE
Sandoz	Aspirin/dipyridamole	25 mg/200 mg; extended-release capsule	1/18/2017
Renaissance	Methocarbamol	1 gm/10 mL (100 mg/mL); IM-IV solution	1/19/2017
Sagent	Ceftriaxone sodium	EQ 10 gm base/vial; injection	1/20/2017
Lupin	Paroxetine	EQ 12.5 mg base, EQ 25 mg base, and EQ 37.5 mg base; extended-release tablet	1/20/2017
Macleods	Tamsulosin HCl	0.4 mg; capsule	1/20/2017
DFB Oncology	Docetaxel	20 mg/mL, 80 mg/4 mL and 200 mg/10 mL; injection	1/20/2017
Perrigo Israel	Desoximetasone	0.25%; topical spray	1/20/2017
Aurobindo	Dalfampridine	10 mg; extended-release tablet	1/23/2017
Actavis	Dalfampridine	10 mg; extended-release tablet	1/23/2017
Sun	Zolpidem tartrate	6.25 mg and 12.5 mg; extended-release tablet	1/24/2017
Par	Phenoxybenzamine HCl	10 mg; capsule	1/24/2017
Tentative Approvals			
Ohm Labs	Sodium oxybate	500 mg/mL; oral solution	1/19/2017
Amneal	Sodium oxybate	500 mg/mL; oral solution	1/19/2017

FDA's NDA And BLA Approvals

Below are FDA's original approvals of NDAs and BLAs issued in the past week. Please see key below chart for a guide to frequently used abbreviations

SPONSOR	PRODUCT	INDICATION	CODE	APPROVAL DATE
New Drugs				
Teva Branded Pharma	*Vantrela ER* (hydrocodone bitartrate)	Extended-release tablet formulations of the opioid for long-term management of severe pain with abuse-deterrent properties for oral, intranasal and I.V. routes of abuse.	S, 3	1/17/2017
Allergan	*Rhofade* (oxymetazole HCl)	Cream formulation of the topical vasoconstrictor, an alpha$_{1A}$ adrenoceptor agonist, to treat persistent facial erythema associated with rosacea in adults	S, 10	1/18/2017
Synergy	*Trulance* (plecanatide)	Guanylate cyclase-C (GC-C) agonist to treat adults with chronic idiopathic constipation	S, 1	1/19/2017

KEY TO ABBREVIATIONS

Review Classifications	NDA Chemical Types
P: Priority review **S:** Standard review **O:** Orphan Drug	**1:** New molecular entity (NME); **2:** New active ingredient; **3:** New dosage form; **4:** New Combination; **5:** New formulation or new manufacturer; **6:** New indication; **7:** Drug already marketed without an approved NDA; **8:** OTC (over-the-counter) switch; **9:** New indication submitted as distinct NDA – consolidated with original NDA; **10:** New indication submitted as distinct NDA – not consolidated with original NDA

Firms Need To Think Fast As Europe's New Patent Court Eyes December Start

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The committee responsible for preparing Europe for the new Unified Patent Court and Unitary Patent has announced that it expects the court to be up and running in December this year, provided the necessary ratifications and other steps are completed in time. Companies would therefore be well advised to start thinking seriously about how they intend to use the new patent system, particularly as regards existing patents.

Partly as a result of the UK government's recent announcement that it intends to ratify the Unified Patent Court Agreement (UPCA) despite the Brexit vote, the UPC Preparatory Committee says it is "now working under the assumption that the provisional application phase (PAP) will start end of spring 2017, presumably in May." This would mean the UPCA enters into force and the court becomes operational in December 2017.

The PAP allows some parts of the UPCA to be applied early, such as the interviewing and appointment of judges. Importantly for companies and other patentees, a "sunrise period" – expected to begin in September – will allow for the early registration of requests to opt-out existing patents from the new system before the UPC comes into operation.

However, the Preparatory Committee stressed that this timetable was "conditional and provided with the clear disclaimer that there are a number of factors that will dictate whether it is achievable."

The most important factors in meeting these dates are the necessary ratifications of the UPCA and accession to the Protocol on Provisional Application, the committed noted. "If these are not achieved the timeplan will be disrupted." Several states have signed the protocol, including France, Germany and the UK.

Robert Williams of law firm Bird & Bird said that while the timeline could still slip, "the UPC train appears to be well and truly back on the tracks, and users of the European patent system therefore need to start thinking again about how to use the system to their best advantage."

Shutterstock: Kris Tan

RATIFICATION AND BREXIT

In order for the court to go ahead, the UPCA must be ratified by at least 13 countries, including France, Germany and the UK. France has already done so, and German and UK ratifications are expected by April.

Last June's vote for Brexit threw something of a spanner into the works, as it was not certain whether the UK would proceed to ratification. However, the government's November 2016 decision to do so means that the agreement can go ahead as planned, at least until such time as the UK's future participation in the system has been decided.

Bird & Bird noted that in his evidence to the science and technology select committee on Jan. 11, Jo Johnson, minister of state for universities, science and innovation, had said it was possible for the UK to take part in the UPC as the court was not an EU institution and that ratification of the UPCA was independent from the status of the UK as an EU member state.

"Whilst this is correct (the UPC Agreement is an international treaty), the Unitary Patent Regulation is an instrument of EU law based on the Treaty on the Functioning of the European Union," the law firm pointed out.

"Furthermore, the Regulation provides for references to the Court of Justice of the European Union for interpretation of points of Union law. This means that participation in the UPC goes hand-in-hand with being subject to the jurisdiction of the CJEU – something that many supporters of Brexit consider to be a "red-line" – albeit this jurisdiction was not intended by the framers of the UPC regime to provide CJEU control over the majority of substantive patent law."

When pressed on the status of the UPC, Johnson – who took on the IP role from Baroness Neville-Rolfe after her move to the Treasury – suggested that the position of the UK within the UPC post-Brexit, and that of the London arm, would form part of the wider Brexit negotiations, Bird & Bird said. "The UK government therefore seems to be doing what it can to enable to the UPC to come into effect sooner rather than later, and to rely on the Brexit negotiations to ensure continued UK participation in the regime," it added."

From the editors of Scrip Regulatory Affairs. Published online January 23, 2016

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Pediatric-focused safety reviews for various products as mandated by the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act; role of pharmacogenomics in pediatric product development	Pediatric	March 6-7
Strain selection recommendations for influenza virus vaccines for the 2017-2018 flu season	Vaccines and Related Biological Products	March 9
Premarketing and postmarketing data about the abuse of Endo's Opana ER (oxymorphone extended-release), and abuse of generic extended-release and immediate-release oxymorphone products	Drug Safety and Risk Management; Anesthetic and Analgesic Drug Products	March 13-14
Strategies, approaches and challenges in model-informed drug development, including use of physiologically-based pharmacokinetic modeling and simulation throughout a drug's life cycle and mechanistic model-informed safety evaluations	Pharmaceutical Science and Clinical Pharmacology	March 15

Pink Sheet

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