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FDA GMP Warning Letters Review: Rate Soared In 2016 On Sterility And Data Integrity Concerns

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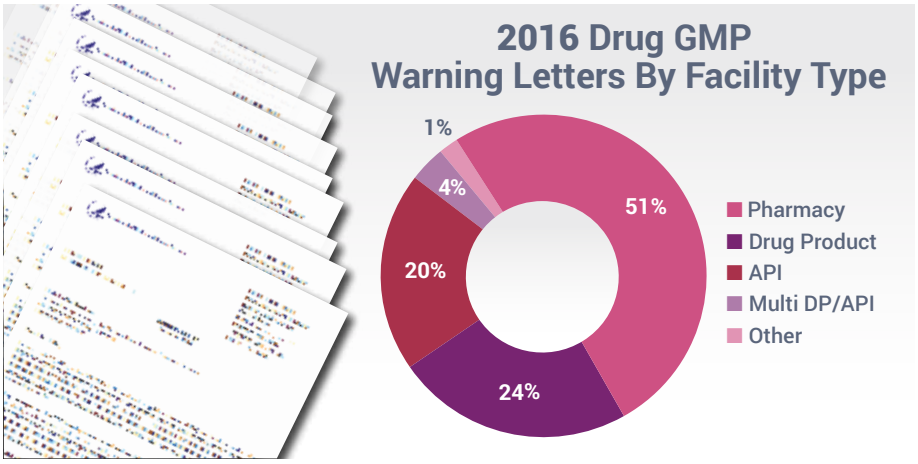

US FDA warning letters related to good manufacturing practices more than doubled in 2016 as the agency continued to crack down on a lack of sterility assurance in domestic pharmacy compounding and a lack of data integrity in foreign active pharmaceutical ingredient manufacturing, and addressed a lack of basic GMP compliance among foreign over-the-counter drug manufacturers.

FDA issued 110 drug GMP warning letters in calendar year 2016, matching a record set in fiscal year 1995 *(Also see "GMP warning letters issued by FDA in FY 1996 drop by 40% compared to previous year." - Pink Sheet, 24 Feb, 1997.)*, and exceeding by 160% the 42 issued in fiscal year 2015. The rate had been trending around 40 during President Obama's second term. *(Also see "FY 2015 Drug GMP Warning Letters Hit Compounders and Foreign Sites" - Pink Sheet, 29 Jan, 2016.)(Also see "FDA's FY 2015 Drug GMP Warning Letters" - Pink Sheet, 29 Jan, 2016.)*

Given that the warning letter rates peaked at 110 with Democrats Bill Clinton and Barack Obama in the White House and dropped below 20 under Republican President George W. Bush, it is possible they could decline again now that the Republican Party has regained the presidency. *(Also see "Enforcement on Steroids: FDA Delivers Twice the Drug GMP Warning Letters" - Pink Sheet, 1 Apr, 2010.)* That said, the Trump administration could just as well find issuing more warning letters to foreign drug manufacturers perfectly consistent with its "America First" foreign policy and trade objectives.

TWO MAIN FACTORS

Regardless, last year's warning letters reflect the latest priorities of those in FDA's enforcement program, which a key enforcement official told lawyers in December boil down to two factors.

"Public health and risk," Tom Cosgrove, director of the Office of Manufacturing Quality in the Center for Drug Evaluation and Research's Office of Compliance, told a Food and Drug Law Institute conference in Washington. "When you're advocating your case to the Office of Compliance, those are two really important things to be talking about, two touchstones that I think will make or break your argument, because that is what, at the end of the day, we're thinking about."

Cosgrove assured an audience of legal experts that in the CDER Office of Compliance, "we don't look for ticky tack or technical violations. We look for violations that matter, and anytime we take an action, we're trying to connect the violation with a public health risk. And when we see

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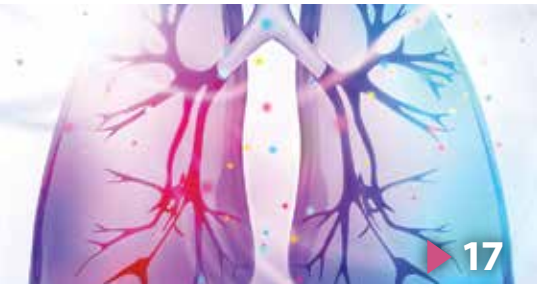
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exclusive online content

Situation Far From Ideal But EU Network Will Survive Brexit

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Brexit undoubtedly will cause some short-term disruption to the EU medicines regulatory network but the network will survive without the UK. That's according to former EMA head Thomas Lönngren. Meanwhile, the timetable for relocating the EMA is likely to be finalized in a few days' time.

Blood Disorders Overtake Cancer On EMA's PRIME Scheme

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uniQure has become the third company to get accepted on the European Medicines Agency's PRIME (priority medicines) scheme for a gene therapy for hemophilia, making hematology-hemostaseology the most common therapeutic areas for products on the scheme.

Gottlieb Advances, But FDA's Future Seems Increasingly Partisan

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Senate committee votes to send the FDA Commissioner nominee to the Senate floor, but with only two Democratic votes.

Express Scripts-Anthem Split Could Signal Positive Trend For Biopharma

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Express Scripts is losing its biggest customer, which could be a sign that plan sponsors are looking for more control over their pharmacy spending -- bad news for the big PBMs but good news for biopharma?

Oncology Combo Drugs Face UK Market Access Disappointment

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New oncology drugs forming new treatment combinations will face a tough ride through England's influential health technology appraisal body, NICE.

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risk, or a plausible and realistic possibility that there could be a patient impact, that's when we're going to take action."

A slide on the screen pointed to four high-risk areas where FDA takes quick action: sub- or super-potent drugs, contamination, sterility concerns and other defects.

Cosgrove was finishing a tour as acting director of the compliance office when he gave those remarks on Dec. 7. The following week, CDER Director Janet Woodcock announced the selection of Donald Ashley as the office's permanent director. Ashley came to the agency from the Justice Department, and with his strong background in international criminal and fraud law enforcement, is sure to continue to emphasize many of the same themes in global supply chain enforcement that were underscored in last year's warning letters. *(Also see "US FDA's New Compliance Chief Donald Ashley Brings International Law Enforcement Experience" - Pink Sheet, 13 Dec, 2016.)*

> New compliance office director Donald Ashley previously was at the Justice Department and is sure to emphasize many of the same enforcement themes underscored in last year's warning letters.

FOUR MAIN THEMES

There were four main groups of warning letter recipients last year:

- Asian API makers with data integrity and facilities maintenance issues.
- Foreign over-the-counter drug product manufacturers that lack GMP basics.
- Sterile injectable drug product manufacturers in the US and abroad that have sterility assurance issues.
- US pharmacies that compound injectable drugs of questionable sterility.

Of 26 warning letters to API firms, 16 focused on data integrity issues, including eight to sites in China and five to sites in India.

The surge in API data integrity warning letters sends a message that drug product firms need to shore up the integrity of their supply chains, particularly where they extend to Asia.

Of 30 warning letters to drug product facilities, 18 went to OTC firms, most of them abroad, for failure to accomplish basic GMP functions. Many of these firms were focused on cosmetics and hygiene products. Some did not appear to realize they were also manufacturing what FDA considers drug products, or to understand what that entails.

Four warning letters went to "multi-product" facilities that manufacture both APIs and drug products.

Of 56 warning letters to pharmacies, 21 went to facilities that had registered as outsourcing pharmacies. The rest asserted they were operating as traditional compounding pharmacies, but FDA found on inspection that many did not qualify. All but two of the pharmacy warning letters focused on sterility assurance issues.

In addition, one repackager and one analytical laboratory received drug GMP warning letters last year.

SOME QUIT RATHER THAN COMPLY

In several cases, foreign manufacturers told FDA they would stop marketing product in the US rather than try to upgrade their manufacturing operations to meet US GMP requirements. For example, Mappel Industria de Embalagens SA of Sao Paolo, Brazil, said it would not have marketed certain products in the US if it had realized FDA regulated them as over-the-counter drugs. Similarly, Laboratoire Sintyl, Geneva, Switzerland, said it would cease manufacturing OTC drugs rather than undergo the substantial quality upgrades required to access the US market.

EDITOR'S NOTE: Changes To Our Annual Warning Letter Analyses

The transition of Informa's pharmaceutical manufacturing quality coverage to the Pink Sheet from the former Gold Sheet has provided an opportunity to update our approach to the annual warning letter analyses. Pink Sheet now analyzes warning letter trends by calendar year versus the previous fiscal year method. Also, Pink Sheet categorizes warning letters by type of facility rather than by type of drug product. So, for example, the Pink Sheet analyzes sterile injectables issues separately for drug product manufacturers and compounding pharmacies.

Let us know how you like the changes, and how we could further improve our warning letter analyses (or other coverage of GMP issues) by email to bowman.cox@informa.com. Thanks!

- **Bowman Cox**, *executive editor, manufacturing quality, the Pink Sheet*

Additionally, numerous US pharmacies shuttered their operations in the wake of FDA inspections that revealed widespread lack of aseptic practices in compounding of injectable drug products.

TOP GMP CITES

The GMP provisions most often cited in drug GMP warning letters last year reflect a major focus in FDA enforcement on sterile compounding.

Compounding pharmacies received 42 of the 51 warning letters that gave the No. 1 citation, Title 21 of the Code of Federal Regulations, Section 211.113, control of microbiological contamination.

Similarly, pharmacies accounted for 39 of the 45 warning letters that cited Section 211.42, design and construction features, and 25 of the 27 warning letters that cited 211.28, personnel responsibilities.

And they accounted for all 28 of the warning letters that cited 211.167, sterility testing.

Note that only 44 of the 56 pharmacy warning letters cited GMP provisions. The other 12 went to facilities that FDA treated like traditional compounding pharmacies that qualify for a GMP exemption under Section 503A of the Food, Drug & Cosmetic Act. In some warning letters, the agency acknowledged the exemption applied; in others the wording was ambiguous.

A second tier of top GMP citations last year stemmed from warning letters to foreign OTC firms. All 16 mentions of 211.34, consultants, were in this category, as the agency strongly advised these firms to retain GMP consultants if they wanted to continue serving the US market (several did not).

Drug product firms also received 12 of the 15 warning letters that cited 211.100, written procedures, and nine of the 13 warning letters that cited 211.22, quality control unit responsibilities.

And although pharmacies predominated in the sterility assurance category, drug product firms added to totals in that area with, for example, nine letters citing 211.113, control of microbiological contamination, and six citing 211.42, design and construction features.

There were no citations of any GMP pro-

CFR Cites In Drug GMP Warning Letters Issued In 2016

CFR	DESCRIPTION	NUMBER *
113	Control of microbiological contamination	51
42	Design and construction features	45
166	Stability testing	31
167	Sterility testing	28
28	Personnel responsibilities	27
192	Production record review	22
165	Testing and release for distribution	18
34	Consultants	16
100	Written procedures; deviations	15
22	QC unit responsibilities	13
67	Equipment cleaning and maintenance	11
160	General requirements; laboratory controls	11
84	Testing and approval or rejection of components	9
68	Automatic, mechanical, and electronic equipment	6
194	Laboratory records	5
137	Expiration dating	4
56	Sanitation	3
94	Drug product containers or closures	3
186	Master batch and control records	3
46	Ventilation and air filtration	2
63	Equipment design, size and location	2
111	Time limitations on production	2
180	General requirements; records and reports	2
188	Batch production and control records	2
198	Complaint files	2
25	Personnel qualifications	1
52	Washing, toilet facilities	1
80	General requirements; control of components	1
101	Charge-in of components	1

* Number of warning letters that cite a specific 21 CFR 211 drug GMP provision

visions for API manufacturers because the GMP regulations don't apply to them. However, as with the traditional compounders, they were cited for violating the statutory prohibition in the FD&C Act against adulteration of drugs.

FULL LISTING; FURTHER ANALYSIS UPCOMING

For a full listing of last year's 110 drug GMP warning letters, complete with facility type, name and location, warning letter and inspection completion dates, and a description of issues addressed, see the table accompanying this article.

Over the next few days, the Pink Sheet will publish more detailed analyses of FDA's 2016 drug GMP warning letters by types of facilities. Look for articles:

- Focusing on the surge in data integrity warning letters to API firms and how it spells trouble for the pharmaceutical industry.
- Examining warning letters to drug product manufacturers and the messages they send to foreign OTC firms on quality and to domestic and foreign drug makers on sterility assurance.
- Reviewing the crackdown on sterile drug compounding that yielded the majority of last year's warning letters.

From the editors of the Gold Sheet.
Published online April 25, 2017

MORE IN THIS SERIES

CLICK

Our analysis of 2106 warning letter trends includes articles taking a closer look at these topics:

- **FDA's 2016 Drug GMP Warning Letters**
- **API Supplier Warnings Surge On Data Integrity Concerns**
- **Foreign Drug Product Firms Hit Hard On GMP Basics**
- **Compounding Pharmacies Drew Most FDA Drug GMP Warning Letters**

We have an online page focused on the manufacturing issues. Find it at:
https://pink.pharmamedtechbi.com/manufacturing

Pharma Industry Still Not At 'Tipping Point' In Adopting Continuous Manufacturing

JOANNE EGLOVITCH joanne.eglovitch@informa.com

The pharmaceutical industry and regulatory authorities agree that continuous manufacturing still is in the early stages of adoption, short of a "tipping point."

But while FDA admits efforts to advance continuous manufacturing are stymied by knowledge gaps, a **Pfizer Inc.** executive warns regulators need to work together to develop uniform interpretations of continuous manufacturing, and not doing so could impede adoption.

These assertions were made at the 3rd FDA/Product Quality Research Institute conference on Advancing Product Quality, March 22-24 in Rockville, Md. Regulators from the US, the EU and Japan highlighted some of the initiatives underway to promote continuous manufacturing in their regions. They also described how they are relying on extensive collaboration with industry and academia to help educate reviewers and industry on continuous manufacturing.

In the US, two approvals have been made to date for continuous manufacturing. The first was **Vertex Pharmaceuticals Inc.**'s cystic fibrosis treatment *Orkambi* in in July 2015 and the second was for **Janssen Pharmaceuticals Inc.**'s supplemental new drug application to switch its HIV-1 treatment *Prezista* from batch to continuous manufacturing in April 2016.

Celia Cruz, director of the Office of Testing and Research in FDA's

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The US has seen two approvals for continuous manufacturing: Vertex's Orkambi and Janssen's Prezista.

Center for Drug Evaluation and Research, said to expect some more approvals for continuous manufacturing in the next two to three years. Cruz, who serves on the agency's Emerging Technology Team (ETT, formed in 2013 to promote the use of new technologies in pharmaceutical manufacturing, said there is a "lot of promise in some of these applications coming through. We will be as busy as you are to try to make sure that this becomes a reality."

Rapti Madurawe, division director of the Office of Process and Facilities in FDA's Center for Drug Evaluation and Research said the agency recognized early on that continuous manufacturing needed "significant nurturing" to become a reality, and is conducting an "unprecedented level of external outreach with industry, academia and other regulators."

NOT AT TIPPING POINT

Regulators and several industry members agreed that despite this outreach, uptake has been sluggish.

"I want to look at where we were with continuous manufacturing and I think we are on a journey. In 2017 I think we would place it in a continuum. The science and principles and the feasibility we have seen commercially. Are we there yet? Are we ready to turn the page?" said Diane Zezza, vice-president global regulatory CMC for **Novartis AG**.

"You might say we're are at infancy in emerging technology with continuous manufacturing and we still have quite a way to go before we achieve broad acceptance," Zezza added.

Christine Moore, global head and executive director of CMC policy for **Merck & Co. Inc.**, made a similar observation. "We are now in the cautiously optimistic stage. We have seen some wins related to continuous manufacturing and approvals in certain regions but we are not there yet. I would say that we're not past the tipping point."

"I think we are still at the point where one bad regulatory experience could still shift the balance of industry looking to invest in this new technology," added Moore, formerly acting director of FDA's Office of New Drug Quality Assessment and an early proponent of continuous manufacturing.

She pointed out acceptance is more common now than two or three years ago, when there was "a lot of pessimism with people saying 'yeah, right, I understand where you are going but I don't think this is going to work because it's not value-added.'"

Still, lot of uncertainty remains about continuous manufacturing on both sides.

The industry has questions related to "will this application be approved, what are the expectations for our products and how many questions am I going to get in my application with the new technologies. And from the review side, what should they expect, how will they get the information they need to do an inspection,", Moore said.

One common issue and concern from both sides is that continuous manufacturing involves a "lot more work. We are putting new platforms there. Is it worth the extra work and the extra risk?" she said.

FDA's Madurawe concurred. "We think this is a great benefit for the industry that means that continuous manufacturing is possible and there are no regulatory barriers in implementing continuous manufacturing but we have a way to go. Like Christine said, we are not at the tipping point yet. There are big opportunities to do more."

FDA ON LEARNING EVOLUTION OF CONCEPTS

Cruz said FDA has made great strides already over the past five years in advancing a regulatory framework for continuous manufacturing. Yet, she admitted the agency is working from a limited knowledge base.

"For us to admit that we have limited experience takes some guts, but here it is. This is why we have the commitment to take some time to do this. We consider this a learning experience in FDA, the industry and academia," Cruz said.

> Companies should talk with FDA before submitting continuous manufacturing applications, FDA's Madurawe advised.

She added FDA has evolved its thinking on continuous manufacturing, with early discussions focused on return on investment and the definition of a batch. "Five years ago how would we define batch? We got a little hung up about that in the beginning. At the end, we moved on to early discussions on sampling frequency and residence time distribution."

Currently, discussions focus on model maintenance. "We are having a lot of discussions about this. This is now," Cruz said.

There also are conversations on material attributes, excipients and run time. Not discussed yet are some higher order principles in continuous manufacturing such as advanced process control and harmonization.

DON'T LET FEAR OF QUESTIONS STOP ADOPTION

Madurawe said the industry should not be afraid when FDA asks questions on continuous manufacturing applications, and should not interpret questions to mean lack of regulatory support. The agency, after all, still is in the learning mode.

In fact, she said, it's important for the conversation with FDA about continuous manufacturing applications to begin before they're submitted. At the conference, she said, there was a question about FDA being prepared for all the applications that are currently in the pipeline.

"We are extremely well prepared and trained to handle that and handle more, but we are not at the point where we are at a plug-and-play stage where companies can just drop their applications without any prior conversations," Madurawe said,

"Questions facilitate shared learning of new concepts and help reach consensus and lead to first-cycle approval. Do not let fear of questions impede the adoption of continuous manufacturing," she added.

Noting that knowledge gaps in the industry have yet to be overcome in advancing continuous manufacturing, she said, "The current workforce is trained in batch manufacturing," not continuous

manufacturing.

For example, manufacturers need to train employees in advanced process monitoring and multivariate approaches for assessing process and product quality, and in using predictive models to support real-time release testing.

Additionally, having the statistical skills to handle the huge amount of data emanating from continuous processes also would be useful, an area where academia can help in training and educating the future workforce, she said.

Madurawe also said the industry is underutilizing PAT tools, which could help ensure that processes are in control in real time, a "real asset" in continuous manufacturing.

EMA AND JAPAN: NO ROADBLOCKS

Like FDA officials, representatives from the EU and Japan said they are encouraging the pharmaceutical industry to submit applications for continuous manufacturing.

Dolores Herman, a European Medicines Agency quality specialist, said although specific guidance is not available, existing guidance supports this approach.

Herman said these EU guidances address continuous manufacturing:

- International Council on Harmonization's Q8, Q9, Q10 and Q11 guidelines, because the principles they set forth apply to enhanced development;
- EU guideline on process validation, which in 2014 introduced the concept of continued process verification;
- EU guideline on real-time release testing;
- EU guideline on manufacture of drug product, which is currently under revision;
- EU guideline on chemistry of new active substances, published in November 2016;
- EU guideline on use of near infrared spectroscopy, which was revised in 2014;
- European Pharmacopeia (PhEur) chapter on chemometrics;
- A quality-by-design question-and-answer guide that resulted from a joint EMA/FDA QbD pilot; and
- GMP annexes 15 and 17.

In addition, Herman said multiple regulatory platforms, tools and incentives promote continuous manufacturing. These include scientific advice from EMA's Committee for Medicinal Products for Human Use, where members offer advice on appropriate tests and studies to support continuous manufacturing; the PAT team, which supports process analytical technology and QbD activities in the EU; the Innovation Task Force, a platform for early scientific dialogue; and the EMA SME office, which offers dedicated support to small and medium pharmaceutical companies.

Those efforts have borne fruit, she said, as the PAT team and pharmaceutical manufacturers have had several discussions and several requests have been made for scientific advice on continuous manufacturing. Two applications have been submitted in the EMA's centralized procedures and one is under the EMA-FDA QbD pilot program.

PMDA is collaborating with the Japan Agency for Medical Research and Development to study continuous manufacturing and is providing training to GMP inspectors.

Herman said while experience is limited to date, EMA recommends early dialogue with regulators during development of continuous manufacturing.

JAPAN ENCOURAGES CONTINUOUS MANUFACTURING

Yoshihiro Matsuda, a senior scientist for quality at Japan's Pharmaceuticals and Medical Devices Agency, said the agency supports the development of continuous manufacturing and is collaborating with outside working groups to ensure it is adopted. "We are learning about CM technology," he said.

"PMDA would like to encourage industry to introduce this innovative manufacturing technology," Matsuda said, adding that adopting continuous manufacturing means "avoiding poor quality, avoiding scale-up issues, and reducing inventory."

PMDA is collaborating with the Japan Agency for Medical Research and Development to study continuous manufacturing and is providing training to GMP inspectors. PMDA is also collaborating with the Japan Society of Pharmaceutical Machinery and Engineering to provide training to reviewers on PAT and multivariate analysis.

He said PMDA also established the Innovative Manufacturing Technology Working Group (IMTWG) within PMDA in July 2016 to propose a regulatory framework for continuous manufacturing. The working group consists of Matsuda and three others who represent PMDA's offices of new drugs, regulatory science, and manufacturing quality and compliance.

The IMTWG activity plan is to organize face-to-face meetings with FDA and EMA, visit continuous manufacturing sites and collaborate on a national research project on pharmaceutical quality control. It plans to publish a draft points-to-consider guidance on continuous manufacturing later this spring.

REGULATORY DISCONNECTS HURT CM

Despite encouragement to embrace continuous manufacturing, one pharma industry official questioned whether it is worth the investment if regulators create unnecessary hurdles to register products.

Roger Nosal, vice-president and head of global CMC for Pfizer, said the firm decided not to pursue a continuous manufacturing

submission for a well-established high-volume product in 2005 because the global regulatory requirements were cost prohibitive.

"The regulatory hurdles to get this approved would have been immense. We figured it would take seven years to get approved globally and it would cost us twice what it would have saved us," Nosal said

However, the situation has improved over the past decade, partly due to to improved receptivity from regulators as well as improved quality assurance and flexible manufacturing capacity, he said.

Because of these more favorable business conditions, Pfizer is pursuing portable, continuous, miniature and modular (PCMM) system as a platform for specific products, Nosal said.

PCMMs, flexible mini-factories that can be installed into existing warehouse spaces and used for development and commercial manufacturing, use PAT and advanced process control (APC) for real-time monitoring. *(Also see "Industry Proponents Make the Case for Continuous Manufacturing" - Pink Sheet, 29 Apr, 2015.)*

"This is a very nice and compact manufacturing suite that can be carried on a semi-trailer and they can be installed and moved around as necessary," Nosal said.

"Because it is portable, you can do a lot besides direct compression. Our plan is to get this registered pretty soon. We have come a long way. We decided it is much better to do continuous manufacturing now than it was 10 years ago. It was too much of a regulatory burden," he added.

Pfizer intends to register PCMM for a new product candidate during the next 18 months.

Yet Nosal said Pfizer anticipates similar regulatory challenges it encountered previously since few precedents are set and health authorities have not established definitive regulatory position on certain issues.

For example, there is still some regulatory uncertainty about the definition of a batch, lot traceability, batch uniformity, process upsets, the ability to change batch size, differentiating APC from PAT monitoring, the lifecycle control of raw materials, site transfers, inspections, compendial criteria and the volume of submission data. Each regulator has different definitions of these terms.

"The definition of a batch is still essentially an issue, yet we are much closer to figuring out what that is. Lot traceability is a big deal but it has always been a big deal," Nosal said.

"What I worry about with continuous manufacturing, because it is new and it is a little bit complicated to understand initially, is that if we don't start to think about this sooner we will wind up having multiple views of what continuous manufacturing is and we will be establishing different continuous manufacturing criteria."

TOO MUCH INFORMATION

Nosal also noted regulatory challenges that are part of a larger problem of recent global regulatory trends.

These include "unpredictable application of ICH guidelines, increased requests to review GMP information, divergent expectations for starting materials controls and requests for even more stability data, and differing specifications," he said.

There was some discussion during the meeting that ICH may adopt continuous manufacturing as a work item. Moore said there are plans to add continuous manufacturing as a work item on the ICH agenda, and that a decision will be made on this in June or July.

Nosal pointed out another problem is differing inspection outcomes. He said at one of Pfizer's sites in 2016, four regulatory authorities made a total of 173 inspections.

"They all gave us different observations and in some cases contradicted each other. This doesn't help. With continuous manufacturing, we are definitely going to need inspections, and we are going to need inspections that are good inspections."

Nosal said requests for CMC information have grown tremendously over the past 20 years and that much of this information is not relevant. "I should not have to be providing cleaning validation and providing all executed batch records for products."

"When I started in regulatory in 1994 and I filed a CMC section around the world, this was about 1,000 pages of CMC information for a small molecule. This was about six volumes for a biologic. Now we are filing on the order of about eight or nine volumes for a small molecule and about 26 volumes for a biologic. That is a lot of additional information and data. This is creating a burden for all of us. There has to be a better way."

"When the rubber hits the road and we actually file a submission, that is when you find out if things are going to work. We have to start encouraging these discussions not just among ourselves, but internally and externally with the regulators so that the regulators are privy to all of the things we are doing."

CM FULLY INTEGRATED BY 2030

Other pharmaceutical officials predicted full uptake of continuous manufacturing is inevitable, but will take time to reach full adoption.

Robert Meyer, a chemical engineer for Merck, said early supporters of continuous manufacturing "will be most likely to win the largest benefits by shaping the way we adopt this new technology."

He predicted continuous manufacturing will be fully integrated into the pharmaceutical industry by 2030. "If the food industry can adopt continuous manufacturing systems in producing potato chips, so can the pharmaceutical industry."

Meyer based some of his projections on how much time the industry took to adopt hot melt extrusion, a technique used to process formulations containing polymers into sustained-release products. The number of hot melt extrusion patents issued for pharmaceutical applications grew from 13 in 1995 to 25 in 2005.

"We have seen a couple of approvals and the adoption curve is showing … by 2020 most of the industry will be invested and by 2025 the ICH countries will be accepting of continuous manufacturing and by 2030 roughly 30 years after we started it should be globally accepted," Meyer said.

From the editors of the Gold Sheet. Published online April 25, 2017

FDA's Worst Case Scenario: Supreme Court Might Defer To It On Biosimilars

BRENDA SANDBURG brenda.sandburg@informa.com

US Supreme Court justices seemed to disagree on whether a biosimilar sponsor must wait until FDA approval to provide notice it intends to market its product and whether the sponsor must hand over its application and manufacturing process information to the innovator.

During oral arguments April 26 in **Sandoz Inc.** v. **Amgen Inc.**, Chief Justice John Roberts Jr. and Justices Anthony Kennedy and Stephen Breyer appeared to favor Amgen's view that 180-day marketing notice should come after FDA approval as they questioned how one could know what the biosimilar is until it is licensed.

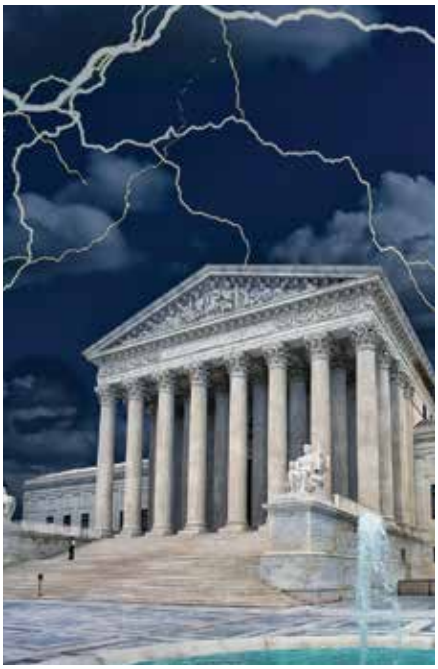
In contrast, Justice Neil Gorsuch appeared inclined to allow earlier notification, noting that remedies exist if the biosimilar sponsor provides a defective notice. He also pointed to remedies if the sponsor declines to give its application and manufacturing information to the innovator, which suggests he may decide the sharing of this information is optional. Justice Sonia Sotomayor also noted that the innovator can obtain the biosimilar sponsor's information by filing a declaratory judgment action and obtaining it through discovery.

Breyer was the most direct in expressing his views on the issues. A system was supposed to be set up "where you've put tremendous incentives on people to negotiate and to work it out in an orderly way," he said. Can you "just gut it by simply filing your commercial notice on day two?"

Justice Kennedy said "the 180 days has to run from some time, and it seems to me that it has to run from the time that it's licensed."

BIG QUESTIONS STILL UP THE AIR

The court is considering two questions about the requirements of the Biologics Price Competition and Innovation Act (BPCIA): Does a biosimilar sponsor have to wait until FDA approval to provide 180-day notice of its commercial marketing? And is participation in the patent dispute resolution process known as the patent dance mandatory?



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> "It's hard to divorce a right from its remedy," Justice Neil Gorsuch said.

The outcome of the case will determine whether biosimilar sponsors have to wait six months after approval to launch their product and how patent litigation will be handled. The case is crucial for innovators and biosimilar sponsors and drew numerous amicus briefs from stakeholders. *(Also see "Ringside For Zarxio At Supreme Court: Biosimilar Stakeholders Line Up" - Pink Sheet, 20 Apr, 2017.)*

As for how the court will rule, Irena Royzman, a partner at Patterson Belknap Webb & Tyler who represents **Janssen Biotech Inc.** in biosimilar litigation, said it is hard to tell what they are going to do from oral arguments.

Courtenay Brinckerhoff, a partner at Foley & Lardner, commented in an email that from the questioning she would not be surprised if the justices decide to require marketing notice after FDA approval and hold that the biosimilar sponsor's provision of its application and manufacturing process information is not optional.

CALLING ON FDA

Justice Breyer expressed discomfort at deciding the issues and repeatedly suggested that FDA resolve questions about the statute through rulemaking.

"Now we are being asked to interpret very technical provisions that I find somewhat ambiguous and am operating in a field I know nothing about. But it's going to have huge implications for the future. So why isn't the way to go to ask the agency to issue some regulations?" Breyer said. "Then we see their interpretation, you all will be able to argue that their interpretation exceeds the statutory delegation. And by doing that, we would have a better picture."

Justice Kennedy also alluded to FDA's involvement in the process, noting that the information exchange begins 20 days after the agency notifies the biosimilar applicant that its application has been accepted.

"It seems to me, certainly, it would be within its authority, or it would be a sensible thing for it to say – and they have a regulation – if you don't do that and we've told you to do that, we're going to delay the review process," he said.

Assistant to the Solicitor General Anthony Yang told the court that Congress had separated FDA from this process and that the agency had been petitioned to do some rule-making on the statute and declined to do so.

Amgen submitted a petition to FDA in October 2014 requesting FDA to require biosimilar sponsors to certify that they will provide the reference product sponsor with a copy of their application and manufacturing process information. FDA denied the petition in March 2015 noting that the BPCIA does not require the agency to impose this certification as part of the biosimilar review process. *(Also see "Sandoz's Biosimilar Launch Eyed For May 11 Or Earlier, Absent Court Injunction" - Pink Sheet, 26 Mar, 2015.)*

For years, FDA has felt overly entangled in legal machinations stemming from its review of small-molecule generics, even as the agency emphasized it had a solely ministerial role in Orange Book listings. The design of biosimilar pathway – with its more cut-and-dry exclusivities and leave-it-to-the-courts attitude on patents – was greeted with relief at FDA. The agency now seems in the somewhat unusual position of not appearing to want authorities that the Supreme Court might bestow upon it, especially since they would add to the already long list of biosimilar policies FDA has to develop.

> "Justice Sotomayor asked about the remedy if a biosimilar applicant complies with the patent dance and the innovator does not. "All incentives have a way of failing. Just look at our society," she said.

'INCENTIVES HAVE A WAY OF FAILING'

Sandoz and Amgen are challenging a July 2015 decision by a divided three-judge panel of the US Court of Appeals for the Federal Circuit. The panel concluded that the statute's patent dance provisions are optional since the statute imposes consequences if the biosimilar sponsor fails to turn over its application and manufacturing process information to the innovator, i.e., the innovator can sue for infringement. The panel also found that a sponsor had to wait until FDA licensure of its biosimilar to notify the innovator of its intent to market. *(Also see "Biosimilar sponsors can avoid 'patent dance' in US, but innovators win extra exclusivity" - Pink Sheet, 22 Jul, 2015.)*

Sandoz had declined to provide Amgen with its application and manufacturing process information for its *Zarxio* (filgrastim-sndz), a biosimilar to Amgen's *Neupogen* (filgrastim) and gave Amgen early notice of its commercial marketing. Sandoz petitioned the Supreme Court to review the Federal Circuit's opinion on launch notification. Amgen opposed Sandoz's petition but asked the court to review the patent dance provision if it agreed to Sandoz's request. The court agreed to review both issues.

The justices asked the most questions of Sandoz's attorney Deanne Maynard, a partner at Morrison & Foerster. By contrast, Amgen attorney Seth Waxman, a former Solicitor General and partner at Cutler Pickering Hale and Dorr, spoke at length without interruption.

During an exchange with Maynard, Justice Sotomayor asked what the remedy would be for the biosimilar applicant if it complies with the steps of the patent dance and the innovator does not. Maynard replied that "the statute provides powerful incentives for the sponsors to continue through the process."

"All incentives have a way of failing. Just look at our society," Sotomayor responded.

'SHALL' MEANS SHALL BUT REMEDIES ARE KEY

One question at issue in the case is whether the word "shall" in the statute means "must" or "may." The BPCIA states that the biosimilar applicant "shall provide" its application and manufacturing process information to the reference product sponsor.

Justice Gorsuch told Waxman "let's say I spot you on that" and "shall" means shall. He said one still can't determine what the provision means without looking at what remedies are permitted.

"It's hard to divorce a right from its remedy, isn't it, and to understand the contours of the right," he stated. And if the BPCIA provision "gives you a certain right to information, we usually understand the right in the context of the remedy provided."

Gorsuch also asked Waxman why an innovator couldn't seek a declaratory judgement if the biosimilar applicant provides insufficient notice.

Waxman replied that you can't provide notice of something when you don't know what's going to happen. He said FDA may require lots of amendments to the application, noting that in this case there were 30 amendments made from the time the application was filed until it was granted. He said that if FDA approves something different than what the application was, the innovator sponsor has to be given time to figure out what FDA has approved and a district court judge has to have time to evaluate the patents and decide if there is infringement.

The justices spent time discussing state law and preemption although the parties had not briefed them on this issue. In its 2014 suit against Sandoz, Amgen asserted claims of unfair competition for unlawful business practices under the California Business and Professions Code. The district court dismissed these claims since it found Sandoz did not violate the BPCIA and the Federal Circuit affirmed the dismissal. Waxman noted that the California statute makes it a violation of state law to fail to comply with federal mandates, including the BPCIA.

Gorsuch asked what happens when there is a claim under state law that no one has argued is preempted. Yang said that if you're complying with the federal statute there is no state law claim as the state law claim "is predicted on violating the federal law."

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Samsung's Renflexis: Second US Biosimilar To Janssen's Remicade, With A Few Firsts

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Photo credit: Janssen

US commercialization of infliximab-abda prior to the outcome of appeals on the '471 patent would be an at-risk launch, Janssen said.

Samsung Bioepis Co. Ltd.'s *Renflexis* (infliximab-abda), approved by FDA April 21, becomes the fifth biosimilar licensed in the US but still has its share of firsts.

It is the first biosimilar approved by FDA without an advisory committee review. It's also the first time in the nascent US market that a single novel biologic (in this case, **Janssen Biotech Inc.**'s TNF-inhibitor *Remicade* (infliximab)) has served as the reference product for more than one licensed biosimilar.

In addition, the Renflexis approval comes in the apparent absence of patent litigation between the biosimilar and reference product sponsors, an anomaly among the early biosimilars.

FDA approved Renflexis for seven indications on the Remicade label. (*See box.*) The biosimilar is not approved as an interchangeable.

As with **Celltrion Inc.**'s biosimilar *Inflectra* (infliximab-dyyb), which was approved in April 2016 and also references Remicade, the Renflexis label does not include Remicade's pediatric ulcerative colitis indication, which is protected by orphan drug exclusivity until September 2018. But like Inflectra, Renflexis' labeling contains language suggesting the biosimilar is safe and effective for this other pediatric use. *(Also see "Inflectra Label Not Exactly Silent On Remicade's Orphan-Protected Claim" - Pink Sheet, 5 Apr, 2016.)*

MOVING AHEAD WITHOUT AN ADCOMM

Renflexis (previously referred to as SB2) is the first biosimilar to receive FDA approval without facing advisory committee vetting.

FDA officials generally have committed to holding advisory committee reviews for the first proposed biosimilar to a given reference product. For example, the Oncologic Drugs Advisory Committee will convene May 25 to discuss **Hospira Inc.**'s (**Pfizer Inc.**) *Retacrit*, which could become the first biosimilar of epoetin alfa (**Amgen Inc.**'s *Epogen*, **Johnson & Johnson**'s *Procrit*).

However, agency officials have suggested that public reviews for subsequent biosimilars to the same product might be skipped unless the applications raise scientific issues that warrant public discussion.

The Renflexis approval demonstrates the agency is sufficiently comfortable making its biosimilar approval decisions on its own without the time and expense involved in bringing its external experts to the table. *(Also see "Biosimilars In 2017: Crowded US FDA Review Queue, Key Legal Decisions" - Pink Sheet, 24 Jan, 2017.)*

The agency's growing experience with biosimilar reviews also has led to questions about the usefulness of the advisory committee process for such products.

The panel reviews to date have been largely rubber-stamp affairs, with FDA only bringing forward those products for which it is satisfied that the analytical data demonstrate high similarity. Furthermore, the agency has spent much of its time at those meetings having to explain the biosimilar development paradigm and respond to committee members' questions and confusion about the concepts of biosimilarity, interchangeability and automatic substitution. *(Also see "Biosimilar Advisory Committee Reviews: Necessity Or Nuisance?" - Pink*

Sheet, 20 Jul, 2016.)

That's not to say the Renflexis application didn't hit some bumps in the road. The original user fee date was in January. FDA extended the goal date by three months following Samsung Bioepis' submission of additional data about the product's manufacturing process. *(Also see "Keeping Track: A Blizzard Of Submissions And A Small Flurry Of Approvals" - Pink Sheet, 5 Feb, 2017.)*

Labeling likely was a relatively easy task with Renflexis given the template set with the Inflectra approval. Renflexis' label largely mirrors that of Remicade and Inflectra, although the Samsung Bioepis product is the only one of the three labeled in accordance with FDA's Pregnancy and Lactation Labeling Rule.

Like Inflectra and the other approved biosimilars, Renflexis' nonproprietary name carries a distinguishable, four-letter suffix. The suffix "-abda" appears to be sufficiently devoid of meaning to satisfy FDA's final guidance on biologic product nonproprietary naming, released in January. *(Also see "Biologic Product Naming: US FDA Sticks With Suffixes 'Devoid Of Meaning'" - Pink Sheet, 12 Jan, 2017.)*

However, FDA continues its disparate application of the provisions in the final guidance, and the August 2015 draft version preceding it. The agency has approved four novel biological products in 2017 but did not require a suffix in the nonproprietary names of any of them. *(Also see "Novel Biologics In US Might Not Start Getting Suffixes Until August" - Pink Sheet, 5 Apr, 2017.)*

OCTOBER LAUNCH IS POSSIBLE

Renflexis marks Samsung Bioepis' first US product approval. The biosimilar was approved in the EU in May 2016 under the trade name *Flixabi*.

Merck & Co. Inc. is responsible for commercializing Renflexis in the US. Celltrion's US commercialization partner, Pfizer, launched Inflectra in November at a 15% discount to Remicade.

A Merck spokesman declined to comment on a price or launch date for Renflexis.

"In accordance with the Biologics Price Competition and Innovation Act (BPCIA), Merck may only launch Renflexis in the US after a mandatory 180-day notice period following FDA approval," Merck said. "As such, we are not commenting on price at this time. We will provide the WAC price at time of launch."

If Samsung provided Janssen with 180-day notice immediately after approval, Renflexis could launch in mid-October.

However, the US Supreme Court is scheduled to hear oral arguments April 26 in the **Sandoz Inc.** v. Amgen case over whether a biosimilar sponsor must wait until after FDA approval to provide 180-day notice of commercial marketing of its product. The high court also will consider whether participation in the BPCIA "patent dance" is mandatory or optional. *(Also see "Ringside For Zarxio At Supreme Court: Biosimilar Stakeholders Line Up" - Pink Sheet, 20 Apr, 2017.)*

There does not currently appear to be US patent litigation between Janssen and Samsung Bioepis over Remicade.

"We are not aware of any patent litigation in the US over SB2," a Samsung Bioepis spokesman said.

In litigation with Celltrion and Pfizer, Janssen has appealed a federal court ruling that invalidated patent No. 6,284,471, which covers the infliximab anti-TNF antibody, for obviousness-type double patenting. *(Also see "Pfizer Eliminates Roadblock To Remicade Biosimilar Launch" - Pink Sheet, 17 Aug, 2016.)*

Janssen also has sued the Inflectra partners on a cell culture media patent, No. 7,598,083. *(Also see "Biosimilar Litigation: Genentech Avastin Suit Tossed; Janssen Remicade Case Uncertain" - Pink Sheet, 3 Mar, 2017.)*

A Janssen spokeswoman said the company would continue to defend its intellectual property rights. "We are continuing the appeal process in the proceedings defending our '471 patent, and await the outcome of these appeals. We view a commercial launch of infliximab-abda prior to the outcome of these appeals to be an at-risk launch."

"We are committed to ensuring patients and physicians have easy and affordable access to Remicade," Janssen said. "We believe that stable patients should be maintained on the therapy that works for them. Samsung's biosimilar infliximab-abda is similar, but not identical, to Remicade. No product has been approved for interchangeability. Samsung's biosimilar infliximab-abda has had limited postmarketing experience in EU markets since its approval last year."

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RENFLEXIS' INDICATIONS

- Crohn's disease
- Pediatric Crohn's disease
- Ulcerative colitis
- Rheumatoid arthritis in combination with methotrexate
- Ankylosing spondylitis
- Psoriatic arthritis
- Plaque psoriasis

EU Approval Recommendations: Strong Showing From Orphans & Biosimilars

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The European Medicines Agency's main scientific committee, the CHMP, made 11 recommendations for drug approval at its April meeting, including four orphan drugs, three biosimilars, and two generic medicines. Two of the orphan products benefited from an accelerated review.

This was the largest number of positive opinions delivered by the CHMP so far this year: the numbers in the first three months were six, six and eight respectively. The figures also show that orphan drugs continue to account for a significant proportion of recommendations: eight of the positive opinions delivered so far this year have been for rare disease indications.

Biosimilars too are looming large, at five recommendations to date in 2017, from a total of just two companies: **Sandoz Inc.**'s etanercept and two rituximab applications in April, and **Amgen Inc.**'s two adalimumab products – versions of **AbbVie Inc.**'s Humira – in January. The CHMP has recommended one drug for conditional approval so far (in February) and one under exceptional circumstances (March) and OKd 12 extensions of indication.

On the less positive side, four approval applications have been withdrawn this year, but on the other hand the committee delivered no negative opinions at any of its first four meetings. This trend could change, though, if the CHMP, as expected, gives the thumbs down to **XBiotech Inc.**'s colorectal cancer antibody at its May meeting. The company said it was "unlikely" that a positive CHMP opinion would be forthcoming, and that "additional steps would need to be taken to potentially gain marketing approval."

> CHMP has recommended five biosimilars in 2017, all from either Sandoz or Amgen.

APRIL MEETING HIGHLIGHTS

Highlights of the CHMP's April meeting included positive opinions for **Sanofi**'s Kevzara (sarilumab) for the treatment of rheumatoid arthritis and **Almirall SA**'s Skilarence (dimethyl fumarate) for psoriasis.

The four orphan drugs were:

Biogen Inc.'s Spinraza (nusinersen) for patients with spinal muscular atrophy, and **BioMarin Pharmaceutical Inc.**'s Brineura (cerliponase alfa) for neuronal ceroid lipofuscinosis type 2 (CLN2) disease, both of which benefited from an accelerated review; **Pfizer Inc.**'s Besponsa (inotuzumab ozogamicin) for acute lymphoblastic leumemia; and GMP-Orphan SA's Cuprior (trientine tetrahydrochloride for Wilson's disease, a rare autosomal recessive inherited disorder – this was a hybrid application using the results of preclinical tests and clinical trials for the reference product as well as new data.

BIOSIMILARS

Gains made recently by biosimilar versions of blockbuster drugs in the EU continued with CHMP recommendations for three products from Sandoz: Rixathon and Riximyo (both rituximab; reference product Roche's MabThera), and Erelzi (etanercept), a biosimilar of Pfizer/Amgen's Enbrel.

The two rituximab products have the same indications, except that Rixathon has the added indication of chronic lymphocytic leukemia (CLL). Asked why this was, a Sandoz spokesperson said: "Based on potential patent implications in some European markets, two applications support our goal of providing biosimilar rituximab to as many appropriate patients as soon as possible. At this time, we cannot comment further on the specific details of this regulatory submission."

If the rituximab recommendations are followed by marketing authorization by the European Commission, they will join **Celltrion Inc.**'s biosimilar product Truxima, which was approved in February this year. Three other rituximab biosimilars are under review by the CHMP. As for Erelzi, this would be the second etanercept biosimilar to gain approval, after **Samsung Bioepis Co. Ltd.**'s Benepali (which was authorized in January 2016).

The two generics OKd in April were **Mylan Laboratories Ltd.**'s Febuxostat Mylan (febuxostat) for the prevention and treatment of hyperuricemia, and Lucane Pharma's Ucedane (carglumic acid)

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for the treatment of hyperammonemia due to N-acetylglutamate synthase primary deficiency.

WITHDRAWALS, HARMONIZATION RECOMMENDATIONS

The product that was withdrawn from the review process in April was a solithromycin product filed by Triskel EU Services Ltd on behalf of Cempra Pharmaceuticals Inc. The product was intended for the treatment of community-acquired pneumonia, inhaled anthrax and inhaled tularemia. The application was withdrawn after the CHMP had evaluated the initial documentation provided by the company and formulated a list of questions. At the time of the withdrawal, the company had not responded to the questions.

Explaining the reasons for the questions, the CHMP said it was concerned that not enough data had been provided to support the product's use in inhaled anthrax and inhaled tularemia, and that it might cause liver damage. It also had concerns about the active substance manufacturing process, "which did not exclude the presence of impurities," while the sterility test "was not considered valid."

Triskel said its decision to withdraw the application was based on a request from the US Food and Drug Administration to provide additional safety data for approval purposes, and that it planned to include these data in a new EU marketing authorization application.

The CHMP also recommended harmonizing the labeling for **Bristol-Myers Squibb Co.**'s etoposide products, Etopophos and Vepesid, which were approved via national procedures in the EU, and which have divergences in the product information in the various member states.

The need for harmonization was identified by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), and in October 2015 the commission referred the matter to the CHMP.

The areas of the product information that have been harmonized for each of the products include the indications (e.g., testicular, small-cell lung and non-epithelial ovarian cancer; Hodgkin's and non-Hodgkin's lymphoma; and acute myeloid leukemia), posology and method of administration, contraindications, special warnings, and side-effects.

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EMA May Clash With Ethics Committees If It Asks For Earlier Neonatal Trials

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The European Medicines Agency's paediatrics committee (PDCO) may come in conflict with ethics committees if, as part of an ongoing review initiative, it decides in favor of asking companies to initiate neonatal studies earlier under the provisions of the EU Paediatric Regulation.

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Currently, the agency defers neonatal studies until the drug is shown to be safe and effective in adults, but it has found that waiting for data to be generated in older age groups often appears to be of limited use. As a result, the EMA is re-considering when it is most appropriate to grant deferrals in order to address the findings of a recent report that questioned the wisdom of granting lengthy deferrals for neonatal studies. *(Also see "EMA Reviews Experience With Deferring PIPs: Will it Result In Earlier Pediatric Trials?" - Pink Sheet, 20 Apr, 2017.)*

If, as a result of this review, the EMA decides in favor of requiring earlier neonatal studies, it may well be that such studies get turned down by ethics committees, according to Geneviève Michaux, a partner at Brussels-based law firm Mayer Brown. She noted that there have already been instances of ethics committees rejecting some studies required by the PDCO on ethical grounds.

This raises the question of who has competence over ethics. "Is it for the PDCO or the ethics committees to decide… on ethical issues? Should the ethics committees' review be limited to adult clinical trials?" Michaux asked.

Requiring earlier pediatric studies may also pose liability risks for companies. Michaux noted that companies would not want to conduct studies in neonates – or any other pediatric subset – before having sufficient confidence in the safety and/or efficacy of the product, and this confidence comes from the adult data.

By asking companies to start studies in neonates earlier, "the EMA would in essence force them to incur risks" that could result in significant financial, reputational and legal liability. "No company should be forced to take such risk, especially with neonates… In such a case, the ethics committees' appreciation should pre-

vail," Michaux told the *Pink Sheet*.

The industry, for its part, has stated that deferrals are "critically important" to protect the pediatric population and are granted for "sound, justified and scientific reasons". Agreeing with the industry's position, Michaux noted that most companies want to complete pediatric investigation plans (PIPs) as soon as possible because this allows them to gain various rewards and incentives offered under the Paediatric Regulation.

"If a company request[s] a deferral for a neonate study, it generally is because it encounters one or more problems… If the problem is lack of sufficient certainty about the safety and/or efficacy of the product… and the ethics committees agree with the company's position, [then] the EMA should not be allowed to force companies in conducting the paediatric studies. Or else the EMA should logically agree to take over the risks and liability associated" with those studies, Michaux noted.

LENGTHY DEFERRALS: ONGOING ISSUES

Granting lengthy deferrals for neonatal studies, particularly in oncology, is part of a larger ongoing issue. "There have been complaints, especially from the field of neonatality and oncology, that pediatric medicines are not coming on to the market quickly enough, and those complaints have reached the European Parliament, which asked the [European] Commission to remedy the situation," Michaux said. She believes that the EMA's initiative is aims to address this issue.

Michaux said that deferrals are also needed because the PDCO sets very high parameters for pediatric trials and a "long time [is] required to complete them." For example, recruiting five neonates for a study on a product to treat a rare disease may be very challenging not only due to the small size of the overall patient population, but also because of parents' unwillingness to have their children participate in such a trial, she noted.

In addition, there have been instances of the EMA asking various companies to undertake similar pediatric studies with products in the same drug class. This can make it tougher for companies to find investigators or recruit patients. "This is an important ongoing issue, especially for SMEs. There is no obvious solution to this problem except staging the deferrals for the different products concerned," Michaux noted.

Pediatric studies may also be discontinued if the development of the product is abandoned or if the product is no longer covered by a supplementary protection certificate. As companies are not legally obliged to inform the EMA about PIPs that are discontinued, Michaux said the agency does not have accurate data on discontinued trials.

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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				
Silvergate	Xatmep (methotrexate)	2.5 mg/mL oral solution treatment of pediatric patients with acute lymphoblastic leukemia as a component of a combination chemotherapy maintenance regimen and management of pediatric patients with active polyarticular juvenile idiopathic arthritis who are intolerant of or had an inadequate response to first-line therapy.	S, 3	4/25/2017
Biologics				
BioMarin	Brineura (cerliponase alfa)	Recombinant form of human tripeptidyl peptidase 1 (TPP1) as enzyme replacement therapy for treatment to slow loss of walking ability in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known TPP1 deficiency.	P	4/27/2017

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

AstraZeneca's Tagrisso On Course To Indian Debut, Affordability Vow In Tow

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AstraZeneca PLC's *Tagrisso* (osimertinib) has cleared an key hurdle on its path toward approval in India after a subject expert committee (SEC) recommended marketing authorization of the product with a local clinical trial waiver. Such a waiver typically helps cut time to the market, and AstraZeneca indicates that it expects to stick with its "affordability" commitment with respect to the product's pricing for Indian patients.

Tagrisso is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an appropriate test, whose disease has progressed on or after an EGFR tyrosine kinase inhibitor (TKI) therapy.

The recommendation by the SEC has is subject to the condition that AstraZeneca conducts a Phase IV clinical trial. The protocol for the study is required to be submitted to the office of the Drugs Controller General of India (DCGI) within six months from the date of approval for marketing in the country, details in the minutes of a recent SEC meeting said.

India currently follows a three-tier review for clinical trials, under which applications are initially evaluated by specialized SECs, which advise the Indian regulator on trial-related permissions as part of the layered approval process. The recommendations of the SECs are vetted by a technical review committee and finally cleared by an "apex committee."

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India currently follows a three-tier review for clinical trials, with applications initially evaluated by specialized SECs, which advise the Indian regulator on trial-related permissions as part of the layered approval process.

GLOBAL DATA, ASIAN PATIENTS

Tagrisso, which has been approved in over 45 countries, was also the first AstraZeneca therapy to be cleared recently under China's new priority review pathway. *(Also see "Multinationals, Patients Benefit From New Approvals As China Speeds Reviews" - Scrip, 11 Apr, 2017.)* Last month, **AstraZeneca PLC** said that that the US FDA had granted "full approval" for Tagrisso 80mg once-daily tablets; it is the first and only approved medicine in the US indicated for NSCLC patients who have tested positive for the EGFR T790M mutation. Tagrisso was granted fast track, breakthrough therapy and priority review designations by the US FDA, and received accelerated approval in 2015 based on tumor response rate and duration of response.

In India, AstraZeneca had presented global safety and efficacy data including data from patients of Asian origin.

"After detailed deliberation, the committee opined that there is no effective therapy available for NSCLC patients (EGFR T790M mutation) who have developed resistance to TKIs. Therefore, the committee recommended for grant of import and marketing of the drug with local clinical trial waiver," the SEC (oncology and hematology) said at its meeting on March 21.

AstraZeneca told the Pink Sheet that in all the three phases of the AURA clinical studies, Asian patients constituted over 55% of the enrolled patient population.

"Phase 3 of the AURA study, demonstrated superiority of osimertinib over chemotherapy in EGFR T790M mutation-positive NSCLC signifying a new standard of care for patients with resistance to EGFR TKI," the company said.

Lung cancer is the leading cause of cancer related mortality world-wide and amongst males in India. About 85% of lung cancers are NSCLC and adenocarcinoma is one of the more common forms of NSCLC.

"EGFR mutations are observed in NSCLC adenocarcinoma and is more common in Asian population, ranging from 25-60%. Nearly two thirds of these patients, whose disease progresses after treatment with

an EGFR TKI, develop the T790M mutation," the company added.

Asked about ensuring the availability of the requisite test in India to confirm eligibility for treatment with Tagrisso, AZ said that T790M can be tested through both tissue biopsy and liquid biopsy (ctDNA).

"Molecular diagnostics that identify certain biomarkers for delivering targeted treatments has an important significance in cancer care today. T790M mutation status is critical for the identification of patients who will benefit from osimertinib. AstraZeneca is committed to collaborate and partner with various stakeholders to ensure both awareness and access to T790M testing so that the right patient gets the right treatment."

PRICING APPROACH

Pricing of innovator medicines is always a thorny issue in predominantly out-of-pocket (OOP) markets like India, but AstraZeneca has indicated that it will factor in the affordability aspect while setting prices of Tagrisso when approved. Out-of-pocket payments account for more than 80% of all private spending in India, where patients foot more than 62% of the country's entire healthcare bill. *(Also see "The BRIC/MIST Playbook: Flexibility And Sticking It Out" - Scrip, 9 Nov, 2016.)*

Asked whether it would consider a tiered pricing approach in India or a patient assistance program for products like Tagrisso, since the US price of the product is estimated at around $12,750 for a month's supply, AstraZeneca explained that it prices its medicines based on the "magnitude" of innovative scientific advancement, the "value" it brings to patients and society, the development program "depth," and the local health infrastructure and economic context.

"In India, subject to regulatory approvals, AstraZeneca is committed to have price points and programs that take into consideration the affordability for Indian patients. In the past, AstraZeneca has always introduced innovative products in India such as *Brilinta, Forxiga* and *Onglyza* in accordance with these factors," the company told the Pink Sheet.

In 2015, AstraZeneca's Forxiga, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, was introduced at around INR43 ($0.67 at the time) per dose for 10mg in India – "competitively" priced with other innovative anti-diabetes drugs on the market and a fraction of the product's price in developed markets. *(Also see "Forxiga debuts in India at fraction of global prices" - Scrip, 11 Jun, 2015.)*

From the editors of Scrip Regulatory Affairs. Published online April 25, 2017

UK Election Extends Industry Wait For Accelerated Access Review Response

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The UK government's much awaited response to the Accelerated Access Review (AAR) report – which contains recommendations on bringing forward patient access to drugs by up to four years – will not be published until after the country's snap general election on 8 June.

When the final AAR report was issued in October 2016, the government announced that it would consider the proposals and respond more fully in due course. No formal expected publication date was given, but a spokesperson for the Department of Health has now told the *Pink Sheet* that "because of purdah, which runs until the general election, the AAR government response will now not be published before the election".

The Association of the British Pharmaceutical Industry said it would be "looking for the next Government to respond swiftly to the report and have a clear plan for turning the [AAR] recommendations into reality." Implementing many of the recommendations in the AAR report will be an important step in addressing poor patient access to new medicines in the UK, the ABPI told the *Pink Sheet*.

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Parliament will be dissolved on 3 May and, under what is known as purdah, all major government announcements and consultations will be on hold until the new administration is formed. The UK BioIndustry Association expects the government's response to the AAR report to be published in July, around the same time as the publication of the Life Sciences Industrial Strategy.

The government commissioned the AAR report to enable the National Health Service to embrace new drugs and medical technologies. Among other things, the report recommends creating a new accelerated access partnership to speed up and simplify the process for getting the most promising new treatments and diagnostics safely from pre-clinical development to patients. *(Also see "UK Accelerated Access Proposals Due Out Soon" - Pink Sheet, 7 Sep, 2016.)*

From the editors of Scrip Regulatory Affairs. Published online April 25, 2017

Eteplirsen Revisited? FDA Panel To Weigh Protocol Changes For Two Sarepta Drugs

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Eight months after the controversial approval of Sarepta Therapeutics Inc.'s *Exondys 51* (eteplirsen), the US FDA is convening its external advisors to weigh changes in an ongoing trial involving two of the company's investigational Duchenne muscular dystrophy (DMD) treatments.

On May 18, FDA's Pediatric Advisory Committee and Pediatric Ethics Subcommittee will meet to consider whether in-dwelling drug ports should be allowed for DMD patients in Sarepta's ESSENCE trial. FDA announced the meeting in a notice scheduled to appear in the Federal Register April 25.

"The focus of the committee is to discuss ethical issues related to putting a drug port in patients randomly assigned to the placebo control arm, as use of ports can increase risk of infections," Sarepta said in a statement to the Pink Sheet.

ESSENCE is a double-blind, placebo-controlled trial evaluating two compounds, SRP-4045 and SRP-4053, in DMD patients with out-of-frame deletion mutations amenable to skipping exon 45 and 53, respectively.

The trial, which began in August, is expected to enroll 99 patients, with final data collection for the primary outcome measure estimated for September 2019, according to ClinicalTrials.gov.

Although the ESSENCE trial and the May 18 advisory committee meeting do not directly relate to eteplirsen, issues that arose in the course of FDA's review of that drug, including the long-term use of sham infusions in DMD trials, are likely to be revisited at the meeting on ESSENCE.

The meeting also may reopen some old wounds from the eteplirsen review, which was marked by sharp disagreements between Sarepta, the patient community, and FDA – as well as among agency staff themselves.

WEEKLY INFUSIONS

FDA granted accelerated approval to eteplirsen on Sept. 19 for patients with a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. The approval followed a lengthy and contentious debate within the agency.

The clinical review team and other senior personnel within the Center for Drug Evaluation and Research (CDER) favored a complete response letter, concluding that Sarepta failed to demonstrate substantial evidence of efficacy. However, they were overruled by CDER Director Janet Woodcock, who concluded that the increase in dystrophin production seen with eteplirsen was reasonably likely to predict clinical benefit. Woodcock's decision was appealed to then-Commissioner Robert Califf, who sided with the CDER director. *(Also see "Sarepta's Eteplirsen Approved After Contentious Internal FDA Debate" - Pink Sheet, 19 Sep, 2016.)*

Like eteplirsen, SRP-4053 and SRP-4045 are infused intravenously. In ESSENCE, study participants will be randomized to weekly infusions of one of the drugs (depending upon genotype) or placebo for two years.

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Issues that arose during FDA's review of eteplirsen, including concerns about long-term use of sham infusions in placebo-controlled trials, are likely to be revisited even though ESSENCE does not involve the exon 51-skipping drug.

Patients who complete the two-year, placebo-controlled portion of the study will be eligible to enroll in an open-label extension, during which all participants will receive active study drug.

The ESSENCE trial is currently recruiting at 14 sites in the US and one in the UK, according to ClinicalTrials.gov. Sarepta said it expects the trial to be fully enrolled by the end of the year.

PLACEBO CONTROL AT HEART OF PORT ISSUE

The ESSENCE protocol negotiated between FDA and Sarepta prohibits the use of in-dwelling ports for intravenous infusion.

A source said although ports were optional in the eteplirsen studies, they were prohibited in ESSENCE due to patient community concerns that requiring study participants on the placebo arm to receive intravenous saline for up to two years would be unethical.

The Jett Foundation, a DMD patient advocacy group, said it was unable to find another pediatric trial in a condition with morbidity and mortality comparable to that of DMD that similarly used a two-year placebo arm.

The foundation made FDA advisory committee history when it was allotted time during Sarepta's presentation at an April 2016

meeting to show data on eteplirsen patient outcomes. *(Also see "Duchenne Group's Presentation Is Milestone For Patient Involvement" - Pink Sheet, 2 May, 2016.)*

"Originally this issue was brought to the surface because of the two-year placebo," the foundation said. "There were concerns that children would need ports and that they were going to be getting trial drugs and normal saline for those ports."

However, some ESSENCE study participants and their families have reported challenges receiving weekly infusions in the trial due to difficulties with peripheral venous access. The foundation said it has heard from at least a half dozen pats in ESSENCE with such difficulties.

"We need to find a way to make it as easy as possible for these boys and young men to participate in a potentially life-saving trial," a foundation representative said.

21 CFR 50.54

"If an IRB does not believe that a clinical investigation within the scope described in 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of 50.51, 50.52, or 50.53, the clinical investigation may proceed only if:

(a) The IRB finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:

(1) That the clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or

(2) That the following conditions are met:

(i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 50.55."

An FDA determination to allow ports would not automatically implement the change at every trial site, PPMD said.

IRB REFERRAL PROCESS

The May 18 advisory committee meeting was triggered by what a source said is a little-used process, an IRB referral under 21 CFR 50.54 submitted by an ESSENCE study site. (*See box.*)

"The site submitted the IRB referral to the FDA's Office of Pediatric Therapeutics (OPT) to modify the ESSENCE protocol to allow for ports after concerns raised by the study's principal investigator that the protocol as it currently exists can cause severe harm to trial participants because it does not allow for ports," the Jett Foundation said.

The Pediatric Advisory Committee and Pediatric Ethics Subcommittee "will discuss, evaluate, and develop a recommendation around whether the protocol should proceed as modified by allowing the option for ports in the study," the group said.

It appears that the meeting will not follow the standard advisory committee format for a product-specific review. Presentations by FDA, the principal investigator and a DMD parent are planned, followed by an open public hearing. This will be followed by Sarepta's presentation and then advisory committee discussion, according to a blog posting by Parent Project Muscular Dystrophy (PPMD).

DECISION RESTS WITH COMMISSIONER

The public docket for the meeting will close May 19.

"Following the meeting and the closing of the docket, a decisional memo will be sent from the Office of Pediatric Therapeutics to the FDA commissioner," PPMD said. "FDA commissioner will then be briefed on the issue and will make a decision as to allow for an amendment to the protocol to allow for the option of an in-dwelling port – or not. The letter to the commissioner will be public and posted on the FDA website."

PPMD said any decision to allow ports would be considered "permissive."

"Each trial site's IRB would then have an opportunity to review the revised protocol and make a determination locally as to whether to amend their site's protocol to allow for in-dwelling port use," the group said. "A determination by the FDA would not automatically implement a change at every trial site."

The committees' deliberations could have implications for other investigational DMD drugs that are given intravenously as well as for intravenous drugs developed to treat other rare pediatric diseases.

REVISITING ETEPLIRSEN DISAGREEMENTS?

While the advisory committees are being convened to consider the allowance of ports, ethical issues related to the use of a two-year placebo control in the ESSENCE trial are likely to arise.

The ability to conduct a placebo-controlled trial was a point

of disagreement between FDA staff and Sarepta representatives during the development and review of eteplirsen. Internal FDA documents showed the agency repeatedly urged the company to conduct a placebo-controlled trial. However, Sarepta took the view that such a study would be unethical in light of the drug's promising early clinical trial results and said an agency bioethicist agreed with that assessment.

FDA and Sarepta also disagreed about the use of ports in long-term placebo controlled studies for eteplirsen. While the company asserted that placebo-controlled trials were infeasible because long-term administration of placebo to children through central venous catheters was unethical, FDA disagreed that such studies could not be done and recommended other types of access devices that do not enter central veins be used.

The confirmatory trial required to convert eteplirsen's accelerated approval to regular approval does not employ a placebo. Rather, the randomized trial is comparing the approved eteplirsen dose to one that provides a significantly higher exposure.

Sarepta said that if the advisory committee advises against the use of drug ports in the placebo arm of ESSENCE, "the trial will continue as designed, with patients receiving once weekly intravenous (IV) infusions in all three study arms. This will be followed by an open-label extension period in which all patients will receive open-label active treatment for up to 96 weeks."

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Capricor Eyes RMAT Designation Based On Interim Phase II Data

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Capricor Therapeutics Inc. is considering whether to seek the US FDA's Regenerative Medicine Advanced Technology (RMAT) designation, a breakthrough therapy designation or both for CAP-1002 (allogeneic cardiosphere-derived cells) in the treatment of Duchenne muscular dystrophy (DMD) based on positive interim results from the ongoing 12-month Phase I/II HOPE clinical trial.

Los Angeles-based Capricor designed CAP-1002 to improve cardiomyopathy, which increases as DMD progresses, but in addition to reducing cardiac scarring, a single treatment with the cardiac progenitor cell therapy improved skeletal muscle function in the HOPE study. The company is not only considering RMAT and breakthrough therapy designations, but also plans to speak with the FDA about allowing its next clinical trial to serve as a pivotal study to support potential approval, since the cell therapy appears to repair – rather than just slow or stop – the progressive muscle degeneration caused by DMD.

An RMAT designation for CAP-1002 would be one of the first granted by the FDA under the still very new RMAT program (formerly known as RAT), which was created under the 21st Century Cures Act.

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Only two RMAT designations have been publicly disclosed to date.

The first was granted to **Humacyte Inc.** for its human acellular vessel product candidate known as *Humacyl* in March. *(Also see "US FDA First's RMAT Designation: Humacyte Got A 'Quick Response'" - Pink Sheet, 26 Mar, 2017.)* More recently, **Enzyvant Sciences GMBH** revealed on April 17 that the FDA granted both an RMAT designation and a breakthrough therapy designation for RVT-802, a tissue-based biologic therapy for the rare congenital immunodeficiency disease known as complete DiGeorge Syndrome (cDGS). *(Also see "Keeping Track: US FDA Expands Indications For Roche Tecentriq, Lucentis, Approves Second Infliximab Biosimilar" - Pink Sheet, 23 Apr, 2017.)*

"RMAT has been built for us, because we have a cell therapy," Capricor President and CEO Linda Marban said in an interview. "We're evaluating internally if we want to do both or just RMAT, which allows us to take advantage of a smaller field of competitors than a breakthrough therapy designation."

Marban also noted that the company will apply for a priority review voucher (PRV) under the FDA's program awarding the coupons to manufacturers of drugs that treat rare pediatric diseases – an initiative that expires in 2020. *(Also see "Sponsors May Race For Rare Pediatric Voucher Designations As*

Deadline Nears" - Pink Sheet, 22 Dec, 2016.) With a breakthrough or RMAT designation propelling its CAP-1002 development program in DMD forward, Capricor could have the PRV in hand before the rare pediatric disease program expires, depending on how quickly the company can complete its forthcoming pivotal trial, which it expects to begin before the end of 2017.

RESULTS OFFER HOPE IN DMD

The randomized, open-label Phase I/II HOPE study enrolled 25 patients aged 12 and older who had cardiomyopathy secondary to DMD as evidenced by scarring in four or more left ventricular segments. All patients in the study remained on the standard of care, consisting mainly of steroid therapy, but 13 patients received a single dose of CAP-1002 (75m cells) infused into each of the three main coronary arteries.

Safety and tolerability within 72 hours of infusion is HOPE's primary endpoint (*see table*). There were no treatment discontinuations or deaths in either arm of the study and the most common treatment-emergent adverse events (TEAEs) were mild or moderate, including atrial fibrillation (20%) and nasopharyngitis (16%) in patients who received CAP-1002 cells. Atrial fibrillations were described as asymptomatic and self-limited, occurring only during CAP-1002 infusions.

Secondary endpoints to be measured at 12 months include cardiac structure measured by MRI, quality of life according to the Pediatric Quality of Life Inventory and a composite of various functional measurements, including the Performance of the Upper Limb (PUL) test.

Capricor reported on April 25 that MRI tests at six months post-infusion showed statistically significant improvements in systolic thickening in the interior wall of the heart for DMD patients treated with CAP-1002 versus patients in the standard of care group (p=0.030). Differences in middle and distal upper limb muscle function also were improved in the treated patients, according to a PUL responder analysis (p=0.045). Improvements in other cardiac and skeletal muscle measures were observed and described as "consistent with a treatment effect," including differences in cardiac scarring (p=0.09).

Marban said the skeletal muscle improvements observed in HOPE and in previous preclinical studies in mice go far beyond the improvements in function that would be expected in boys and young men with DMD who had improved cardiac function.

"We're very enthusiastic about what these data hold," she said, noting that for the advanced DMD patients enrolled in HOPE – 70% of whom were non-ambulatory and confined to a wheelchair – these kinds of skeletal muscle gains could allow an immobile boy to feed himself, comb his own hair or hug his mother without assistance.

CUTTING RISK OF CARDIAC DEATH

Study participants ranged from age 12 to 25, but the median age was 17.5 in the standard of care arm and 18 in the CAP-1002 group. Children with DMD generally end up in a wheelchair during their teens and aren't expected to live past their 20s, because of heart disease that eventually results from the degenerative neuromuscular disease.

Marban noted that the boys and young men treated in the HOPE study represent a segment of the DMD population that has not been able to participate in clinical trials, because it was thought that their advanced disease state would mean they were too far gone to see an improvement in their condition. However, she said the six-month results exceeded expectations.

"Thought leaders that we spoke with said that if you could slow the decline, you'd have a hit, and this may reverse scarring," Marban said. "We're very excitedly moving into our next trial, which is potentially registrational. And we know that the peak of effectiveness of a single dose is at three months, so we're going to build in multiple doses."

The six-month data comprise an interim look at HOPE; the trial will continue through 12 months, so the results could change when the study is completed.

The company will also test a systemic intravenous infusion of CAP-1002 rather than a local infusion of cells in the coronary region. The Phase I/II results showing efficacy in heart and skeletal muscles repeat another finding from preclinical studies, which was that Capricor's cells distribute exosomes throughout the body, which leads to repair in muscles beyond cardiac muscles. Those effects also improved over time with additional injections of CAP-1002. The impacts on DMD patients in HOPE were observed regardless of an individual's genetic mutation.

The next human study is expected to enroll less than 100 DMD patients, but the final number and trial design will depend on discussions with the FDA. However, Capricor expects to be able to start the study before the end of 2017.

The California Institute for Regenerative Medicine (CIRM), the state's stem cell research funding agency, provided a $3m grant to support the HOPE study, which covered half of the clinical trial's costs. Cure Duchenne Ventures and Coalition Duchenne also provided financial support while Parent Project for Muscular Dystrophy advised Capricor's clinical trial design and patient recruitment.

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Safety Results At Six Months

ENDPOINT	USUAL CARE (N=12)	CAP-1002 (N=13)
Any TEAE	10 (83%)	11 (85%)
Severe TEAEs	2 (17%)	1 (8%)
Serious adverse events	1 (8%)	3 (23%)
Any drug-related TEAE	NA	8 (62%)
Any procedure-related TEAE	NA	7 (54%)

US FDA Still Waiting For Cures Money, Woodcock Says

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Additional funding through the 21st Century Cures Act for the US FDA to work on several mandates intended to help bring new drugs to market faster does not appear to have arrived yet.

Center for Drug Evaluation and Research Director Janet Woodcock said April 24 that funding through the legislation continues to navigate the federal budgeting process.

"To my knowledge we haven't gotten any funding yet," Woodcock said during the Drug Information Association-FDA Statistics Forum. "We were supposed to get some funding this year … but it's going through various steps. So we don't have it yet."

The question to Woodcock came in the context of the 2016 21st Century Cures Act's effect on FDA staffing. Cures allowed FDA to offer higher salaries, but Woodcock said in the current budget environment things remain largely uncertain.

"The rest of the budget the rest of this fiscal year – and in the budget going forward for the government – is really questionable right now," she said. "And so we don't know it all."

Cures included several mandates for FDA to improve biomarker qualification and the use of real-world evidence in drug development. It also called for enhanced use of patient experience data and guidance on adaptive trial designs. *(Also see "The Evolution Of 21st Century Cures Legislation" - Pink Sheet, 29 Nov, 2016.)*

The bill also gave FDA $500m in additional funding spread over 10 years. FDA was slated to receive $20m of that in fiscal year 2017, which began in October. *(Also see "US FDA Getting More Money Up Front Under Cures Bill Revisions" - Pink Sheet, 30 Nov, 2016.)*

But the agency and rest of the government are operating without a permanent budget. To bridge between the end of the Obama Administration and beginning of the Trump Administration, Congress passed a continuing resolution funding the government through April 28. It included the Cures payment for FY 2017.

Congress now is working to keep the government funded either with a budget for the remainder of the fiscal year or another CR. *(Also see "FDA's Government Shutdown Plan Ready, Just In Case" - Pink Sheet, 19 Apr, 2017.)*

STATISTICIANS RANKS GROW IN 2016

Uncertainty about FDA's budget may curtail some hiring initiatives, but the agency's biostatistics divisions still are growing. Lisa LaVange, director of the CDER Office of Biostatistics said during the conference that nearly 30 new people have been hired since late April 2016, when the previous Statistics Forum was held. She said it was a record year for recruitment.

LaVange also said the agency is seeking two associate directors to handle biosimilars and statistics policy and wants four new deputy directors and four supervisory associate directors.

In addition, the office established an intergovernmental personnel agreement that allows outside experts to work at FDA while on sabbatical or a part-time basis and expand the breadth and depth of the agency's statistical expertise.

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FDA has had problems recruiting executive-level staff, in part because of the salaries it can offer and federal conflict-of-interest rules. *(Also see "CDER's 50 Open Leadership Posts Could Be Bigger Hiring Challenges After Trump Freeze" - Pink Sheet, 2 Feb, 2017.)*

Former FDA Commissioner Robert Califf favored working with other groups within and outside the government so the agency could keep up with the latest scientific advancements. *(Also see "Califf Lowering FDA Drawbridge To Work With External Expertise" - Pink Sheet, 18 Apr, 2016.)*

CURES, USER FEE HIRING AUTHORIZED

FDA also continues to prepare for Cures-related hiring. The agency expects it will need several specialists that it does not normally recruit such as social scientists and big data analysts to develop patient-reported outcome measures and assess real-world evidence, respectively.

It also continues to hire employees as part of the current prescription drug user fee program, although it has yet to find all those mandated. And the agency has committed to adding another 230 employees during the upcoming PDUFA VI cycle, which will begin Oct. 1. *(Also see "User Fees: Should US FDA Incur Penalties For Missed Deadlines?" - Pink Sheet, 26 Mar, 2017.)*

But like nearly all other federal agencies, FDA also has been told to create long-term plans for staff reduction. The Office of Management and Budget encouraged agencies and departments to consider eliminating vacant positions. *(Also see "A Hiring Freeze By A Different Name: OMB Wants Agency 'Workforce Reduction' Plans" - Pink Sheet, 12 Apr, 2017.)*

The directive for long-term staff cuts marked the official end of the federal hiring freeze President Trump implemented upon taking office. *(Also see "US FDA May Find Relief From Trump's Hiring Freeze" - Pink Sheet, 1 Feb, 2017.)* While there were concerns that FDA may be prevented from adding staff mandated in user fee legislation and Cures, the administration decided that those new employees could be brought on board. *(Also see "The Freeze Thaws: US FDA Allowed To Hire Staff For Cures, User Fee Activity" - Pink Sheet, 22 Mar, 2017.)*

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Consumer Business Reliable And Right At Home At GlaxoSmithKline

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GlaxoSmithKline PLC CEO Emma Walmsley says the firm's consumer products business, which she headed until her recent appointment to Glaxo's helm, is a steady revenue source for the firm as well as being one-third of its operating structure.

Walmsley didn't reference her previous post during Glaxo's 2017 first-quarter earnings briefing on April 26, her first as CEO, but her familiarity with the business that markets OTC brands including *Flonase* allergy treatment and *Excedrin* pain relief was clear in her response to multiple questions from analysts about the firm's future as a three-part operation.

The firm's OTC drug and consumer health products business is not leaving as it, along with GSK's vaccines unit, are more reliable revenue drivers than the pharma business, she said.

"We … do see both logic and benefit in being three-business health care company, not least because of some of the uncertainty and volatility that we see in the high-return pharma business. We like to have more certainty in terms of reliable cash flows both from vaccines and consumer," she said.

The consumer unit's value isn't realized entirely separately from the pharma business, though. Walmsley noted Glaxo's pipeline for moving Rx drugs to OTC or nonprescription sales.

"We believe in some of the synergies, both from an operating point of view and a life cycle management point of view, when we look at switches," she said.

CEO Emma Walmsley confirms the importance of Glaxo's consumer business in her first earnings briefing at the firm's helm.

> "We … do see both logic and benefit in being three-business health care company, not least because of some of the uncertainty and volatility that we see in the high-return pharma business."
> – Glaxo CEO Emma Walmsley

SWITCH LAUNCHED DURING Q2

Glaxo's first-quarter consumer business results included sales of its second Rx-to-OTC switch launched in the US in three years, *Flonase Sensimist Allergy Relief* (fluticasone furoate/27.5mcg spray). *(Also see "GSK Aims Flonase Sensimist To Counter Generic Nasal Allergy Competition" - Pink Sheet, 8 Feb, 2017.)* The firm also extended distribution of the original OTC Flonase (fluticasone propionate/0.05mg) intranasal corticosteroid in Canada and Europe during the quarter.

However, the loss of consumer product revenues in Nigeria, where GSK exited in September; a slump in India due to cash shortages caused by the country's demonetization of its ₹500 ($7.70) and ₹1,000 ($15) bills; and a slow allergy season during the January-March period offset the gains to hold growth at 16% based on adjusted currency exchange rates to £2.04bn ($2.6bn), or 2% on constant exchange rates, the firm reported.

Excluding the impact of divesting the Nigeria business, consumer product sales grew at 17% AER, 3% CER, it said.

Oral care products were a key consumer business sales driver, helped by the US launch during the quarter of *parodontax* brand stannous fluoride toothpaste labeled to help stop bleeding gums and continued strong performance by the

Sensodyne line as sales grew 21% AER, 6% CER, to £628m ($810.4m). *(Also see "Glaxo's Parodontax Brings Bleeding Gums Claim To US Toothpaste Battle" - Pink Sheet, 17 Mar, 2017.)*

Sales for the wellness division of the business grew 16% AER, 2% CER, to £1.07bn ($1.4bn) on strong performances by pain relief brands, notably Excedrin (acetaminophen, aspirin, caffeine) and *Fenbid* (ibuprofen). The division's OTC respiratory product sales grew 15% AER, 1% CER, on a stronger flu season behind double-digit growth from the *Theraflu* (acetaminophen, pheniramine, phenylephrine) oral products and *Otrivin* (xylometazoline) nasal spray.

However, gains from those brands largely were offset by a later start to the US allergy season and increased private label competition for Flonase. The brand's sales increased 11% AER, though down 3% CER, despite positive initial launch take-up of Flonase Sensimist, Glaxo said.

In the nutritional products sector, foreign exchange trimmed 8% from sales growth reported at 3% AER to £182m ($235m).

Skin care product sales grew 16% AER, 4% CER to £163m ($210.4m) as international region sales jumped 26% AER, 10% CER, on *Fenistil* (dimetindene) topicals growing 19% AER, 10% CER, with good momentum particularly in the Middle East. Strong international sales of *Lamisil Once* offset the impact of competition in the US and Europe as the line extension for the Lamisil (terbinafine) athlete's foot treatment grew 28% AER, 6% CER. However, *Physiogel* moisturizing products sales were hit by competitor activity in key markets, Glaxo said.

CAUTIOUS OUTLOOK, BUT LEADING

Chief Financial Officer Simon Dingemans said during the briefing that India's cash shortage began to wane during the latter weeks of the quarter, and sales of Glaxo's *Horlick's* nutritional beverages should pick up there during the rest of 2017.

"I think as we move through the course of the year, we are expecting improvements in the Indian position. … We should see that pick up performance," Dingemans said, but he added that, "macro conditions" in emerging markets "remain tough" and warrant "a note of caution in terms of how far much further forward" the business will move.

> The joint venture with GSK is in the catbird seat for considering adding brands from competitors, or acquiring entire businesses that may become available, Walmsley suggested.

Costs from leaving Nigeria also will affect the unit's results through the second quarter, the CFO said. "So, we should see in the second half of the year a bit better performance than we've seen so far, but it does remain challenging," he said.

On the whole, though, Walmsley, who succeeded Andrew Witty as Glaxo's CEO on April 1, sees nothing but opportunity for Glaxo's consumer health business, which also markets **Novartis AG**'s OTCs and nutritionals in a joint venture GSK majority owns and operates. *(Also see "From Witty To Walmsley – The Priorities For GSK's New CEO" - Scrip, 4 Apr, 2017.)*

The JV, **GlaxoSmithKline Consumer Healthcare LP**, is in the catbird seat for considering adding brands from competitors, or acquiring entire businesses that may become available, she said.

"We've structured the JV to allow for potential further consolidation in the industry, which we'd like to be part of to a degree," the CEO said.

"As the leader in the consumer health care sector, we actually keep an eye on what's out there," Walmsley said, adding that Novartis would be part of any decisions for the JV, too.

In a same-day research note, Credit Suisse European Pharma Team analysts said Walmsley "gave a confident performance" during the briefing, including making clear Glaxo's commitment to a three-business structure.

From the editors of the Tan Sheet.
Published online April 27, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Discussion of six drug substances nominated for inclusion on the section 503A Bulk List eligible for compounding: nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide disodium reduced, nettle (Urtica dioica) whole plant, ubiquinol, vanadyl sulfate and artemisinin. Also, discussion of oral solid modified-release drug products that employ coated systems, nominated for the "Difficult to Compound" list.	Pharmacy Compounding	May 8-9
Recommendations on the agency's Innovation Funds work plan as prescribed in Sec.1002 of the 21st Century Cures Act	Science Board	May 9
NX Development Corp.'s 5-aminolevulinic acid hydrochloride powder (for oral solution) for use as an imaging agent to facilitate the real-time detection and visualization of malignant tissue during glioma surgery	Medical Imaging Drugs	May 10
Considerations for evaluation of respiratory syncytial virus vaccine candidates in seronegative infants	Vaccines and Related Biological Products	May 17
Proposed protocol modifications to Sarepta's efficacy and safety study of SRP-4045 and SRP-4053 in patients with Duchenne muscular dystrophy	Pediatric, and Pediatric Ethics Subcommittee	May 18
Puma Biotechnology's neratinib maleate for single-agent, extended adjuvant treatment of adults with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy	Oncologic Drugs	May 24
Emmaus Medical's L-glutamine powder (oral solution) for the treatment of sickle cell disease	Oncologic Drugs	May 24 (afternoon)
Hospira's (Pfizer) proposed biosimilar to Amgen Inc.'s *Epogen*/*Procrit* (epoetin alfa) for all of the indications on the reference biologic's labeling	Oncologic Drugs	May 25

Pink Sheet

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Phil Jarvis, Mike Ward

CORPORATE SALES
John Lucas, Elissa Langer

ADVERTISING
Christopher Keeling

DESIGN
Jean Marie Smith

US
Denise Peterson
Nielsen Hobbs
Mary Jo Laffler

Europe
Eleanor Malone
Maureen Kenny

Asia
Ian Haydock

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