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Gottlieb's Confirmation: He's Willing To Disagree With Trump, Sec. Price

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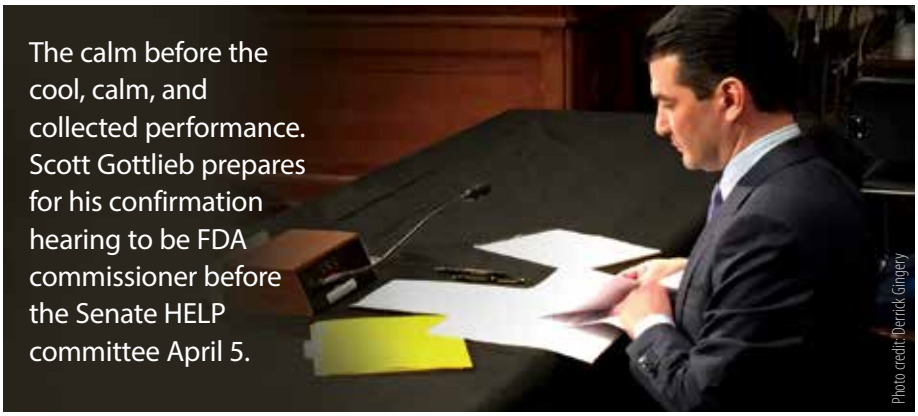

The calm before the cool, calm, and collected performance. Scott Gottlieb prepares for his confirmation hearing to be FDA commissioner before the Senate HELP committee April 5.

Photo credit: Derrick Gingery

Scott Gottlieb's confirmation hearing to become FDA commissioner featured Democrats pressing him to affirm his independence from his potential bosses.

Gottlieb was asked point blank by Sen. Patty Murray, D-Wash., during the April 5 hearing in the Senate Health, Education, Labor and Pensions Committee whether he was "willing to stand up to the administration" if it tries to pressure him.

Gottlieb responded to the committee's ranking member that he is not afraid to speak up and will be guided by the science and expertise of FDA's career staff.

"For those who have worked with me, I haven't been shy about offering my unvarnished advice," he said. "I'm going to continue to offer people my very clear thoughts on whatever issues I'm asked to opine on, including [from] my bosses."

President Trump and other White House staff have made statements about FDA standards that concern a number of stakeholders and lawmakers. *(Also see "Trump Slams FDA Regulations In Joint Session Of Congress" - Pink Sheet, 28 Feb, 2017.)*

Gottlieb also separated himself from Trump on vaccines. When Sen. Christopher Murphy, D-Conn., asked whether Gottlieb would oppose a political panel researching vaccines and links to autism, Gottlieb said the issue has been settled.

"I think we need to come to the point where we can accept no for an answer around this question and come to a conclusion that there is no causal link between vaccination and autism," Gottlieb said. " I have a history of not being shy … about speaking through to power and making my views known … and I will bring the same operating platform to this position."

Trump has hinted that he may create a panel to study vaccine safety that may be headed by a known proponent of vaccines causing neurological diseases like autism. *(Also see "'He Is Very Pro-Vaccine': Trump Mulls RFK Jr. To Chair Commission On Safety" - Pink Sheet, 10 Jan, 2017.)*

Gottlieb also was asked whether he thought the market could judge efficacy in Phase III trials, an idea suggested by another candidate for the commissioner position to make treatments available sooner. *(Also see "Gottlieb Nomination As US FDA Chief Could Signal Changes To Generic Approval Process" - Pink Sheet, 13 Mar, 2017.)* He answered that he believed in the existing law.

"I believe in the gold standard for safety and effectiveness and I believe Congress has delineated a single standard for demonstrating that," he said.

Gottlieb was open to potential changes to the Hatch-Waxman Act to make complex generics easier to move through the approval process, namely involving the instructions for use.

MEASURED DISAGREEMENT ON RESOURCES

Gottlieb was more careful about disagreeing with the administration on issues like the budget.

When Sen. Robert Casey, D-Penn., asked about advocating against a hiring freeze and FDA budget cuts, even if they conflicted with administration views, Gottlieb

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Politics Could Get In Way Of Quick Decision On New EMA Home

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An early decision on the new home for the European Medicines Agency would help to minimize the level of disruption that will be involved in moving the agency from London to somewhere else in Europe when the UK leaves the EU. The EMA and the European Parliament have both called for quick resolution on this, but what you want is not always what you get.

EMA To Speed Up Orphan Approvals By Closing Gap Between CHMP, COMP Opinions

https://pink.pharmamedtechbi.com/PS120375

The European Medicines Agency has initiated steps to ensure that the opinions issued by its human medicines evaluation committee and the orphan drugs committee for certain types of innovative orphan drugs reach the European Commission at around the same time. While the move is expected to facilitate an earlier decision on the marketing authorization applications of such products, industry says it does not go far enough.

Cell Therapies, Biosimilars Boost Biologics Clinical Trials In Korea

https://pink.pharmamedtechbi.com/PS120369

South Korean clinical trial data for 2016 reflects the global boom in biologics R&D and the decline in development of synthetic drugs. A series of clinical trial failures by major South Korean pharmaceutical firms may also have weakened overall drug development activities.

A Look At Payers' Early Game Plans For Driving Biosimilar Use

https://pink.pharmamedtechbi.com/PS120243

Interviews with US payers suggest that at first they are more likely to focus on promoting biosimilars in treatment-naïve patients, as opposed to switching those on branded drugs, according to a new Datamonitor report.

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gave a more measured response.

"I'm going to be committed, Senator, to advocating for a strong FDA," he said. When Casey pressed, Gottlieb added: "I'm going to be committed to advocating for proper resources for FDA and a strong user fee program, making sure that the mandates that you've given FDA are properly resourced and fulfill our mission."

> Asked about his industry ties, Gottlieb said he would have a "process in place ... for helping me to manage whatever recusals I do have to put in place and I will consult with ethics officials."

Casey did not seem pleased with the response. "That wasn't the answer I was waiting for," he said.

FDA's budget is a particular area of concern because Trump has proposed substantial cuts to the remainder of fiscal year 2017 along with an FY 2018 cut to be offset by increases in user fees. *(Also see "US FDA Faces Hiring Slowdown, Funding Cuts In Trump's FY 17 Plan" - Pink Sheet, 28 Mar, 2017.)*

Lawmakers also are worried about the effect of Trump's federal hiring freeze on FDA's ability to add the necessary people to meet mandates in the user fee and 21st Century Cures legislation. *(Also see "US FDA May Find Relief From Trump's Hiring Freeze" - Pink Sheet, 1 Feb, 2017.)*

Gottlieb refused to give his opinion on a decision during his stint as FDA deputy commissioner for medical and scientific affairs to not make **Teva Pharmaceutical Industries Ltd.**'s *Plan B One-Step* emergency contraception over-the-counter. When Murray asked if he thought the decision was a mistake, Gottlieb responded that he would not re-litigate a previous approval.

After Gottlieb left FDA, HHS also overruled FDA's decision to approve the OTC determination. *(Also see "HHS Overrules FDA On Plan B OTC, Sends Teva Back To Drawing Board" - Pink Sheet, 7 Dec, 2011.)*

CONFLICTS CRITICIZED, PRAISED

As expected, Gottlieb also had to address the extensive industry relationships he cultivated during his career. Repeatedly he said public integrity is important and that he did not want his ties to pharmaceutical and other companies to damage confidence in FDA decision making.

Murray asked about how Gottlieb's "unprecedented industry ties" may influence his priorities at FDA.

"I am going to work hard to make sure I preserve my integrity in this role and the integrity of FDA," he responded. "I get it. I understand how important the impartiality of this agency is so that people can continue to have trust in decisions that FDA makes. I'm going to make sure that I have a process in place if I am confirmed into this role in my front office for helping me to manage whatever recusals I do have to put in place and I will consult with ethics officials. This is exceedingly important to me. I want to earn and keep the public's trust."

Gottlieb pledged to divest stock and other interest that he acquired through work with a venture capital firms and bank, as well as resign seats on several corporate boards. *(Also see "Gottlieb's Confirmation: Will Industry Ties Remain A Big Deal After The Hearing?" - Pink Sheet, 3 Apr, 2017.)*

Republicans praised Gottlieb for his experience, highlighting what he was giving up to become leader of FDA.

HELP Committee Chairman Lamar Alexander, R-Tenn., also said Gottlieb's experience allows him to understand the companies and markets that he will regulate.

"I agree with those senators who said we're fortunate that you do have this broad experience," Alexander said. "I like the idea of having someone in your position who is experienced, who recognizes those nuances, who sees the conflicts, who knows what a company may be able to do to create a new drug and how a company may be trying to game the system, who might understand more rapidly than someone who doesn't have your background how to look at a market that doesn't have competition and speed up competition."

Alexander related Gottlieb's industry ties to those of former Commissioner Robert Califf, saying Califf was a better commissioner because of his experience.

Califf also faced a number of questions about his industry relationships during his confirmation hearing. *(Also see "Robert Califf Wants You To Forget His Confirmation Hearing" - Pink Sheet, 16 Nov, 2015.)*

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Complex Generics: Gottlieb Eyes FDA Policy Changes To Speed Approvals

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The US FDA should explore administrative steps within the existing Hatch-Waxman framework to smooth the abbreviated new drug application (ANDA) process for complex generics, but congressional tweaking of the landmark law might be necessary, commissioner-nominee Scott Gottlieb said at his April 5 Senate confirmation hearing.

FDA needs to "develop better scientific principles" for assuring substantial equivalence of ANDA products when traditional measures of bioequivalence may not be adequate, Gottlieb told the Senate Health, Education, Labor and Pensions Committee.

"I think there is opportunity to do that within the framework of Hatch-Waxman," he said. "I would want to challenge the agency to do that, but this might be an area where we need to come back to Congress and have a broader discussion around what that should look like."

Gottlieb suggested the 1984 statute that established the ANDA pathway might need updating to reflect the increasing complexity of products for which generic approvals are sought.

"This is a situation where you have drugs that Congress intended … to be subject to vigorous competition but we didn't envision when we passed Hatch-Waxman because the drugs themselves have gotten more complex," he said.

The challenges with getting generics of complex drugs and drug/device combinations approved have been widely noted by FDA and industry as evidenced by the Generic Drug User Fee Act II agreement, which proposes to create a new set of agency/sponsor meetings around the development and review of such products. *(Also see "Complex ANDAs To Be Allowed Pre-Submission Product Meetings" - Pink Sheet, 24 Oct, 2016.)*

Gottlieb's interest in the area, and his extensive remarks on the subject during the confirmation hearing, could serve to bring a new level of attention to the issue and whet lawmakers' appetite for legislative changes.

TROUBLE DEMONSTRATING EQUIVALENCE

Speeding generic drug approvals was just one of a host of issues that Gottlieb testified about during a nearly two-and-a-half hour confirmation hearing, which also included discussion of FDA's role in combatting opioid abuse, agency workforce issues and implementation of the 21st Century Cures Act.

Gottlieb faced extensive questioning from Democrats on the panel about his ties to industry through consulting arrangements and his work in the venture capital industry. He vowed to be an impartial advocate for the public health and to make decisions guided by science, not political pressure or financial interests.

The former FDA official was expected to face questions about changes to the generic drug approval process given his public calls for ANDA-related regulatory reforms. *(Also see "Gottlieb Nomination As US FDA Chief Could Signal Changes To Generic Approval Process" - Pink Sheet, 13 Mar, 2017.)*

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> "Instructions for use for a drug/device combination needs to be precisely the same for the branded drug and the copy drug in order to go through the ANDA process. There might be an opportunity to relook at that framework."

His comments about the generic drug approval pathway were framed in the context of measures FDA can take to help reduce drug prices. President Donald Trump has repeatedly pledged to bring down the cost of drugs, in part by reducing the tax and regulatory burden on pharmaceutical manufacturers. *(Also see "Carrots and Stick: Biopharma At The White House" - Pink Sheet, 31 Jan, 2017.)*

On the issue of generic drugs, Sen. Todd Young, R-Ind., asked Gottlieb whether there are "certain regulations or guidances you think are particularly burdensome or obsolete that should be withdrawn or significantly revised?"

"One of the issues I've looked at recently is the issue of so-called high value generics or complex generics, where FDA struggles to put certain drugs through the ANDA process because it's difficult to demonstrate substantial equivalence using just the traditional tools, which is bioequivalence and bioavailability studies." Gottlieb said.

In response to a question by Sen. Rand Paul, R-Ky., Gottlieb spe-

cifically cited the challenges of demonstrating substantial equivalence for drugs that act topically, are delivered to the lungs through metered-dose inhalers, or act inside the gut.

Mylan NV's bid for generic approval of one such complex product recently was recently rebuffed by FDA. The company's ANDA referencing **GlaxoSmithKline PLC**'s blockbuster asthma drug *Advair* (fluticasone/salmeterol), which is administered through a metered-dose inhaler, received a complete response letter in late March. *(Also see "Mylan's Generic Advair Delay Gives Leverage To Rivals" - Pink Sheet, 29 Mar, 2017.)* Due to complications inherent in developing generics of respiratory agents, GSK has been able to hold onto market exclusivity for Advair despite US patent expiration.

"I think Congress didn't envision with Hatch-Waxman that certain drugs would have monopolies in perpetuity long after their intellectual property has expired but for the inability of FDA to have a scientific process that can prove interchangeability for those drugs," Gottlieb said. "I think this is an area where we can make a lot of progress."

RETHINKING INSTRUCTIONS FOR USE

When asked by Sen. Al Franken, D-Minn., what FDA can do to reduce the price of drugs such as the opioid overdose reversal agent naloxone, Gottlieb again pointed to the possibility of administrative action to enable approval of complex generics.

Generic injectable versions of **Endo Pharmaceuticals Inc.**'s now-withdrawn branded naloxone product *Narcan* are often packaged with atomizers and administered intranasally by emergency responders, but they have been the subject of steep price increases in recent years.

FDA has approved NDAs for a naloxone auto-injector and a nasal spray specifically for community use, but these products lack generic competition. *(Also see "FDA's Naloxone Product Approval Standards May See Changes" - Pink Sheet, 4 Oct, 2016.)* Other NDA sponsors have encountered regulatory hurdles in reaching market with their naloxone products. *(Also see "Amphastar's Naloxone Nasal Spray Delayed; User Human Factors Study Among FDA Concerns" - Pink Sheet, 21 Feb, 2017.)*

"With respect to naloxone, that falls into the scope of complex drugs that I've talked about here today," Gottlieb said. "It's a drug/device combination. … It's hard to put alternatives through the generic drug approval process. I do think that there are ways that FDA can administratively perhaps, and it might require statute, allow a pathway to make it easier to put generic alternatives to some of these drugs through the generic drug approval process so we can create more competition."

He suggested that one way to help speed competition for such products could be easing the requirement that an ANDA product's instructions for use be the same as that of the reference product.

"Under the current guidelines, the instructions for use for a drug/device combination needs to be precisely the same for the branded drug and the copy drug in order to go through the ANDA process," Gottlieb said. "There might be an opportunity to relook at that framework."

The need for identical instructions for use may be contributing to the delay in generic competition for Mylan's *EpiPen*.

Mylan's price hikes for the branded epinephrine auto-injector, which lacks a generic competitor, have brought congressional hearings and heightened scrutiny of both the pharmaceutical industry's drug pricing practices and FDA's generic drug review operations. *(Also see "EpiPen Outrage In Congress Puts Spotlight On FDA Generic Review" - Pink Sheet, 29 Aug, 2016.)*

PREVENTING 'REGULATORY ARBITRAGE'

Challenges with moving complex generics through the ANDA process are only part of the problem when it comes to high drug prices, Gottlieb said.

In comments that seemed to be a thinly veiled swipe at **Turing Pharmaceuticals AG**'s decision, under the leadership of Martin Shkreli, to aggressively increase the price of *Daraprim* (pyrimethamine) shortly after acquiring the off-patent drug, Gottlieb pointed to delays in competition due to "just the ordinary generic approval process."

"We've seen situations where certain drug markets have fallen to one or two drugs, prices have been raised, and the market isn't self-correcting because trying to get in an application and get it approved could take up to four years," he said.

"You have people who have been able to take advantage of regulatory arbitrage by buying a product that might not face generic competition … jack up the price, and it takes a long time for other people to come into the market even though the high price should be attracting competition. I think that's a solvable problem and something I hope to work on."

CAN HATCH-WAXMAN BE IMPROVED?

Gottlieb suggested Congress may need to re-evaluate whether Hatch-Waxman is achieving the type of market competition that lawmakers originally sought with the law.

The law's co-author, Sen. Orrin Hatch, R-Utah, asked Gottlieb whether "we can improve Hatch-Waxman?"

> "There are opportunities to make sure that Hatch-Waxman is having its intended effect on the market."

"I think that there are opportunities to make sure that Hatch-Waxman is having its intended effect on the market," Gottlieb replied.

"Sitting here today without the benefit of being briefed by the staff at FDA and better understanding these issues, because issues always look different from the inside than they do from the outside, I think that there are opportunities to make sure the law is having its intended impact," he said. "If that requires us to look at certain aspects of the statute, I would certainly come back to Congress and have that discussion."

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OTC Monograph Woes No Surprise To FDA Commissioner Nominee Gottlieb

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FDA Commissioner nominee Scott Gottlieb says the OTC monograph program, a system the agency is looking at modernizing, needed "immediate action" 10 years ago before he left a commissioner's office post.

Gottlieb was asked only one question about nonprescription drugs regulation during his confirmation hearing before the Senate Health, Education, Labor and Pensions Committee on April 5, but it covered a large part of FDA's current concerns about the OTC market.

The monograph system, established in the early 1970s to allow long-used ingredients to remain available and to make additional ingredients available, has stalled under a process that requires notice-and-comment rulemaking for any addition or change. The gridlocked process not only impedes adding OTC ingredients and indications, but also prevents FDA from efficiently responding to problems with monograph products on the market.

Gottlieb, responding to questions by HELP member Sen. Robert Casey, D-PA, said he knew of monograph concerns before he ended his second stint in FDA commissioner's office posts in 2007.

"Anytime a problem persists from when I was there 10 years ago to today it is an indication that I think it requires immediate action," said Gottlieb.

The monograph system, Casey said, is a program "which I think many would argue is ineffective and in need of improvement."

Pointing out that he and Sen. Johnny Isakson, R-GA, are working on monograph modernization legislation, Casey asked Gottlieb to work with Congress on improving the program with changes that would "ensure that both safety and efficacy information is communicated to consumers in a timely fashion."

Gottlieb replied that he is familiar with legislation Congress is working on and he is aware of support at FDA for lawmakers' ideas.

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> "Anytime a problem persists from when I was there 10 years ago to today it is an indication that I think it requires immediate action."

"I think … this is a system that is in need of modernization. So this is something I would be very committed to work with you on if I had the opportunity to be confirmed into this role," he said.

The Consumer Healthcare Products Association recently said it expects a bill soon will be introduced in Congress to allow FDA to add to or change a monograph through administrative orders rather than requiring a rulemaking will authorize a more efficient process for making monograph drug label changes. *(Also see "OTC Monograph Reform, User Fee Legislation Coming 'Any Day' – CHPA" - Pink Sheet, 30 Mar, 2017.)*

CHPA aligns with Gottlieb's prognosis for the monograph program. "We agree that the time to act is now and we are actively engaging with Capitol Hill and FDA now to reform the OTC monograph system. We appreciate FDA's work and attention to make sure the system is more responsive and that it better enables innovation," said John Gay, the trade group's senior vice president for government affairs, in an email.

FDA in 2014 launched an initiative to improve and modernize the OTC monograph system and a separate initiative in 2016 on a potential user fee program to pay for its monograph work. CHPA expects Congress will cover both topics in the pending legislation. *(Also see "'Real Challenge' To Improve OTC Monograph Program Without User Fees – FDA" - Rose Sheet, 16 Jun, 2016.)*

SWITCHES ALSO IN GOTTLIEB'S VIEW

Gottlieb, a physician and currently a resident fellow at the American Enterprise Institute conservative think tank, was a senior advisor to former FDA Commissioner Mark McClellan from 2003-2004 before moving with McClellan to the Centers for Medicare and Medicaid Services as senior advisor and returned to FDA in 2005 as deputy commissioner for medical and scientific affairs for a year and half.

In addition to FDA's monograph travails, Gottlieb is no stranger to the other major piece of the agency's OTC concerns. He was aware soon after his latest departure that approval of additional nonprescription drugs through the Rx-to-OTC switch process had slowed and that some adjust-

ments in that system also could be needed.

After discussion of making drugs available nonprescription but via behind-the-counter sales only flourished with FDA's approval of the original *Plan B* (levonorgestrel/0.75mgx2) emergency contraception in 2007, Gottlieb suggested the agency encourage switch sponsors, in on an ad hoc basis, to submit plans for risk-management proposals, including BTC sales. *(Also see "Behind-The-Counter Guidance Stalled, But Interest Grows To Expand Access" - Pink Sheet, 30 Jun, 2008.)*

The FDA Amendments Act of 2007 gave the agency wider latitude for risk-management requirements on Rx products, meaning FDA still could not require BTC sales for nonprescription drugs and including that limit on consumer access would continue to be voluntary in switch proposals.

Gottlieb's CMS experience also influenced his thinking on making more drugs available nonprescription. Also in 2007, he suggested sponsors work with insurers in advance of nonprescription switches to develop reimbursement plans to benefit consumers, particularly when considering a potential BTC product.

At an industry conference, he said insurers and payers face growing incentives to reimburse consumers for some nonprescription drugs as more drugs become available and as more consumers look first for remedies available without prescriptions. Payers' attitudes have evolved since the OTC switch of *Claritin* (loratadine) antihistamine in 2002 forced consumers to pay more out of pocket than they had in insurance co-pays for the Rx version. *(Also see "Evolving Switch Scene Could Drive Nonprescription Reimbursement – Gottlieb" - Pink Sheet, 9 Jul, 2007.)*

During the HELP hearing, Casey also queried Gottlieb advocating against a hiring freeze and budget cuts, even if it conflicted with Trump administration views. *(Also see "Gottlieb's Confirmation: He's Willing To Disagree With Trump, Sec. Price" - Pink Sheet, 5 Apr, 2017.)*

The committee's vote on Gottlieb is at least two weeks away, according to Chairman Lamar Alexander, R-TN.

From the editors of the Tan Sheet. Published online April 5, 2017

EU National Agencies Prepare For 'Rebalancing' Of Network Post Brexit

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Domestic medicines regulatory agencies throughout the EU are hiring and training extra staff to cover the additional workload that will result from the likely loss of UK expertise and capacity from the European pharmaceutical regulatory network post Brexit. "We're reorganizing ourselves, and there will be a rebalancing of the network" with the departure of the UK from the EU, but the network is "strong enough" to cope. That's what Karl Broich, the head of the German agency, BfArM, told an audience that included hundreds of pharmaceutical industry representatives at this year's European meeting of the Drug Information Association in Glasgow.

It may not be what they want, but Broich said he and his counterparts in the other 26 EU member states "have to prepare ourselves for the worst outcome", that is "a hard Brexit with no co-operation with the UK" after the country leaves the EU.

The UK punches well above its weight in the EU pharmaceutical regulatory network through its regulatory agency, the MHRA *(Also see "UK Regulator Has Key Role in One in Four EU-Wide Approvals" - Pink Sheet, 22 Nov, 2016.)*. There is real concern that, without the manpower and expertise the MHRA currently provides, the remaining 27 member states will struggle to meet their public health commitments in the area of drug regulation and pharmacovigilance. Brexit will also be a huge challenge for the European Medicines Agency, another pillar of the network. The EMA will have to move from its current London base and it fears losing up to half its staff of almost 900 in the process. Industry, among other things, worries that assessment times will slow.

"The UK is the backbone of the network," one former senior regulator remarked to the Pink Sheet on the fringes of the DIA EuroMeeting, which ran from March 29-31. "If you remove the backbone..." He didn't finish the sentence. He didn't need to; his meaning was clear.

> "The challenge at this stage is to get buy-in to the principle that the EU and the UK will be stronger if they continue to find ways to work together."
> – Jonathan Mogford, UK MHRA

Broich was one of seven experts taking part in a panel discussion on the potential impact of Brexit on the established European regulatory environment. He made it clear how much he valued the UK's involvement in the network. Another panellist was Jonathan Mogford, the MHRA's director of policy and chair of the mixed government/industry group on UK drug regulation and Brexit known as the "Deep Dive working group". Mogford said Brexit highlighted the risk to any network of having one member with a role as strong as the one the UK has in this case. Melanie Carr, head of the stake-

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holders and communication division at the EMA and a member of the agency's Brexit task force, referred to the "tremendous input" from the MHRA to the network. All three regulators emphasized the imperative to protect public health.

The Brexit session in Glasgow took place on March 29, the day the UK prime minister, Theresa May, triggered Article 50, formally notifying the EU of the country's plan to leave the bloc and setting the stage for two years of negotiation in the run-up to Brexit in March 2019.

Many - if not all - stakeholders agree that the best outcome in public health terms would be some form of continued regulatory co-operation between the UK and the EU post Brexit. However, this can by no means be guaranteed. As Broich and Mogford said, both sides have to prepare for "no deal" on continuing collaboration, make contingency plans, and recognise that the EU regulatory network will rebalance as a result of the UK leaving the EU.

Estimates suggest the UK is responsible for 20-30% of the workload of the network overall. The Danish agency, the DKMA, has already said it is taking on new staff (*Also see "'Virtually Bribery And Corruption Free' Denmark With Its Clean Canals Says 'Give Us EMA'" - Pink Sheet, 10 Feb, 2017.*). It was "no longer business as usual", Broich told the conference. Others national competent authorities, including BfArM, were also hiring new people, "to train them [and] to prepare for the workload that might come very soon", he said. The German agency has been looking at what might happen if it were to take on "10, 20 or 30%" of the work the MHRA currently carries out for the network. "Everyone in the network is now doing this homework," Broich said. They are also working on knowledge transfer with UK colleagues so as to ensure UK expertise is not lost but remains within the network.

Broich said the network would do everything it could to support the EMA and to prioritize workloads. There would be "no problem" for public health, he said. "Early access to medicines will still be the same post Brexit and safety issues and signals will be dealt with exactly the same as they were before Brexit. We will do our job."

FUTURE ROLE OF MHRA

The role the MHRA will play in Europe post Brexit – if any – is a huge unknown. Through the Deep Dive group, industry and government have been working together among other things to examine the two broad likely outcomes for a post-Brexit regulatory framework.

The preferred outcome, Mogford reiterated, is continued co-operation. "The offer from the UK to continue the regulatory partnership remains firmly on the table and we think it makes very strong sense from a public health perspective."

This would involve "some form of Europe-wide partnership working, where a sovereign UK continues to support the technical scientific assessment work of the wider European regulatory framework." That could be "relatively straightforward," Mogford said, "involving mutual recognition agreements for things like [medical] devices and inspections and agreements on continued shared scientific assessment in some other areas like licensing".

The other potential outcome that is being considered is a "stand-alone" outcome, which might happen if there is no deal. This could involve the UK operating outside the EU framework but perhaps also choosing to rely on some of the decisions that the EU or other regulators take.

There are "compelling public health advantages" to a Europe-wide post-Brexit partnership, Mogford said, adding that Brexit was "entirely consistent with an ongoing regulatory partnership across Europe on both pharmaceuticals and [medical] devices…. If both sides wish it." That, said Mogford, was "very much the logic" behind the prime minister saying that "coming out of the EU is not the same as coming out of Europe."

Mogford clarified in a Q&A session that followed the panel discussion that models that have been used in the past such the European Economic Area were not being sought. In response to a question on this issue from Merete Shmiegelow of Novo Nordisk, he said the challenge would be to find a solution and a way forward that is "specific to the UK and Brexit".

The sense is that technically you can make a partnership work, Mogford said. The challenge at this stage, he continued, is to get buy-in to the principle that the EU and the UK will be stronger if they continue to find ways to work together.

The MHRA official repeated what his boss, MHRA chief executive Ian Hudson, first said several weeks ago, that whatever the outcome, the UK was "not going to be operating to a hugely different set of regulatory requirements." *(Also see "UK Not Planning To Add to Regulatory Burden for Life Science Industry Post-Brexit" - Pink Sheet, 23 Mar, 2017.)*

DAY 1 ANALYSIS PAPER

As well as considering the future role of the MHRA in the EU, the Deep Dive working group has been working on what Mogford described as a "Day 1 analysis paper." Alan Morrison, vice president international regulatory affairs at MSD, the Brexit panel chair, said that Brexit provided an opportunity to create a world-class life science environment for the UK outside the EU. However, he referred to the related change as "profound".

Morrison listed some areas that will be affected, every one of which has "so much detail and so many complications to work through" over the next two years and beyond. The areas were legislation and marketing authorizations; pharmacovigilance; clinical trials; quality assurance; R&D; the supply chain; and intellectual property.

On the topic of supply, Mogford said that ensuring there was an uninterrupted supply of pharmaceuticals in the UK on Day 1 was "absolutely critical".

The other panellists were Virginia Acha, executive director, research, medical and innovation, at the UK Association of the British Pharmaceutical Industry; Elizabeth Kuiper, director of European affairs at the European Federation of Pharmaceutical Industries and Associations; Saad Shakir, director of the Drug Safety Research Unit in the UK; and Nick Meade, director of policy at Genetic Alliance UK. The Pink Sheet will cover other aspects of the discussion in future articles.

From the editors of Scrip Regulatory Affairs. Published online April 4, 2017

Bayer's Adaptive Pathways Experience: 'Disappointing', But Valuable Lessons Learned

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Europe's adaptive pathways scheme has come in for a lot of flak lately, mainly because of concerns over how real world data can actually be used in practice to support the wider use of a drug that has been approved earlier than usual on a limited data package.

Two real-world examples of the potential pitfalls of the adaptive pathways model as experienced by Bayer with two of its products were presented by Regina Seidel, the company's global regulatory strategist, at the recent Drug Information Association EuroMeeting in Glasgow, UK.

Key amongst these pitfalls were a lack of proper discussions with, and divergent expectations among, European health technology assessment (HTA) bodies. But while Bayer eventually pulled its two drugs from the adaptive pathways pilot, all was not gloom and doom because the experience offered stakeholders some interesting lessons for the future, Seidel said.

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As she explained, adaptive pathways is a way of speeding access to potential new therapies in areas of high unmet need by granting an initial license for a small population on limited data and then gathering "real world data" to increase knowledge of the drug's safety and efficacy and extend its use to a broader patient population. A key part of the scheme is parallel scientific advice from the European Medicines Agency and HTA organizations.

Presenting her case study at a DIA workshop on "Value demonstration for regulators and payers," Seidel stressed that she would not identify the two products concerned because they were still in development, although she noted that the first one was an oncology drug which had received early-stage scientific advice and had moved into Phase II planning.

The company applied for the adaptive pathways route for this product and held a stage I safe harbor meeting with the EMA in February 2015. Also involved in the process were five HTA bodies: NICE (UK), ZIN (Netherlands), TLV (Sweden), AIFA (Italy) and G-BA (Germany).

But the experience was "disappointing", Seidel told the meeting. "What should have been a joint discussion about how we proceed and how planning could be adapted on the path forward to extend the knowledge was very much kind of a one-way street."

While the EMA was "really supportive and interested in pursuing the drug for potential conditional marketing approval, the feedback that we received from NICE and the G-BA was that at that point in time they did not support further discussion of what the value proposition could look like for this drug."

The TLV, AIFA and ZIN showed only "moderate interest" in discussing the uncertainties around quantifying that value, and both the EMA and the HTAs expressed concern over the single-arm trials proposed by the company. It therefore decided to pull the product out of the pilot.

SECOND DRUG

The second drug was unusual in that it had already been approved for a different indication and was now in a Phase II study for a new use. Bayer had "quite an interesting stage I meeting" where it was encouraged to come up with further scenario planning for gathering real world evidence and show how this could support the expansion of knowledge of the drug and to present more concrete details of a proposed registry, Seidel observed. "This was for a disease that progresses sometimes slowly and sometimes rapidly, and long-term follow up would be required."

The company held a stage I teleconference in June 2015 at which recommendations were made for stage II discussions, and the stage II face to face meeting took place at the EMA in February 2016. However, again the results were "somewhat disappointing" as "the discussions were not really discussions," but rather a lot of questions regarding the rationale for the choice of endpoints in the ongoing Phase II study, how the disease is being treated in different countries, and how real world data could extend knowledge of the drug, Seidel said.

The company was asked how it would deal with the biases that go along with collecting real world evidence and its limitations, and was also told to provide an economic model for the disease even though this was "a point in time when we were not able to get that immediately." It would have taken another few months to come up with a reasonable approach and that would have delayed things further, Seidel said.

"So that was one of the major roadblocks that prevented us from moving on – we felt that we could not gain any further benefits from any subsequent parallel advice with the HTAs." This product too was removed from the adaptive pathways pilot.

LESSONS LEARNED

Despite these setbacks, though, Seidel said the company had learned a number of lessons. Internally, the projects fostered greater

collaboration with colleagues working in R&D, market access and pricing and reimbursement. "We also saw, particularly in the second case, that even among the HTAs and the EMA there was unanimous understanding that this was an area of high unmet medical need."

And even though this disease involved "very complicated composite endpoints that needed to be qualified," this "allowed our colleagues to come up with a very early value proposition, which usually comes very later in our process. Really, it caused complete new rethinking in our company," Seidel said.

Bayer also gained a valuable understanding of the other stakeholders' perspectives. "We learned that there are very different opinions from different HTAs and this leaves us wondering whether we would ever get a package that leads to convergence. In this case, probably next time we would pick the right indication to allow them to get a better understanding of the endpoints that are appropriate and which comparators are appropriate and relevant for regulators as well as HTAs."

But there are challenges ahead for the adaptive pathways scheme, Seidel said, such as the "substantial" upfront investments needed and the question of real world data collection, data ownership and data methodologies for analysis – "it triggered in our company [the need] to increase significantly the people involved in real world data to work on this."

Moreover, there was often a lack of clear feedback from the HTAs on whether the data proposed would represent adequate real world registry studies, "and the divergence of expectations was something that we did not know how to deal with," she noted.

So while the adaptive pathways concept is a very good one, this was perhaps "just not the right point in time" for Bayer to take part, she said. "There is still a lot of learning to be done, on the how and the what of real world data and its role in decision making as well as on the evidence package and how small it could be." She also questioned whether it was really possible to produce a common evidence package that meets the needs of both regulators and the HTA bodies.

As to whether convergence was possible at an early stage for all HTAs and regulators, Seidel said, "My personal opinion is a clear no, particularly the HTA in Germany: they have the rules of the game, they have the legislation, and the legislation doesn't allow the G-BA to really come up with positive appraisals – that would require even a change in the legislation."

It was Germany's HTA body IQWiG that recently claimed the EMA's report on the adaptive pathways pilot showed that there was no clarity as to how to use real world data to draw reliable conclusions about the benefits and risks of a drug, and said that a halt should be called to adaptive pathways applications until a wider public debate had been held. *(Also see "EMA Defends Adaptive Pathways Against Fresh Attack Following Pilot Report" - Pink Sheet, 11 Aug, 2016.)* IQWiG produces HTA reports on demand for the G-BA.

From the editors of Scrip Regulatory Affairs. Published online April 3, 2017

PATENTS

Ampyra, Patents, And The Perils Of Letting PTAB Get Your Hopes Up

BRENDA SANDBURG brenda.sandburg@informa.com

Acorda Therapeutics Inc.'s celebration in defeating Kyle Bass' challenge of its *Ampyra* (dalfampridine) patents in inter partes review (IPR) proceedings was short-lived as a district court found them to be invalid, clearing the way for possible generic entry in July 2018. The different outcomes show the perils of both pathways for patent owners.

In a March 31 opinion, US District Court for the District of Delaware Judge Leonard Stark ruled that the defendants – **Apotex Inc.**, **Mylan Pharmaceuticals Inc.**, **Roxane Laboratories Inc.** and **Teva Pharmaceutical Industries Ltd.** – had met the burden of proving that four Acorda patents are invalid as obvious. The patents relate to the use

of 10 mg sustained-release formulations of dalfampridine, also known as 4-aminopyridine or 4-AP, to treat walking impairments in individuals with multiple sclerosis.

The defendants "adduced clear and convincing evidence" that a person of ordinary skill in the art "would have been motivated and would have had a reasonable expectation of success to practice and combine each of the limitations of the asserted claims of the Acorda patents," Stark concluded.

"This is not to say that there is no significant evidence of nonobviousness," he added, saying there is merit in many of Acorda's contentions. Of particular note, he said, was the testimony of co-inventor and Acorda CEO Ron Cohen.

"At trial, Dr. Cohen vividly recounted the sometimes harrowing financial risks he and his nascent company took, and the several occasions on which it looked as if his 'bet-the-company' approach had suffered a fatal blow," the ruling states. "It may well be that Dr. Cohen's subjective experience of the 'invention story' was that the purported invention of the Acorda patents was anything but obvious. The court has considered this evidence – but the law directs a different analysis."

"In the end, there is evidence on both sides of the parties' dispute, and this was an eminently 'triable case,'" Stark stated.

But he concluded that based on publications about dalfampridine, a person of ordinary skill in the art would have known in 2004 that 4-AP was known to have the capacity to induce seizures, and would have also known that seizures could be particularly dangerous for individuals suffering from MS and still have motivation and reasonable expectation of success with 4-AP despite recognizing this risk.

ACORDA TO APPEAL, FOCUS ON LATE STAGE PARKINSON'S DISEASE DRUGS

The court upheld the validity of an Ampyra extended release formulation patent, which Acorda licensed from **Elan Corp. PLC** That patent expires in July 2018 so generic versions of Ampyra would be blocked from entering the market at least until then, which is seven years earlier than expected.

The company had reached settlements with seven other generic manufacturers. The first six settlements noted that generic companies could enter at a specified date in 2027, or earlier depending on certain circumstances. The seventh agreement, reached with Apotex in February, permits Apotex to launch its generic version in 2025 or potentially earlier under certain circumstances.

"The company said it has developed contingency plans to address its business needs and objectives in the event of a loss of Ampyra exclusivity and will provide an update after finalizing the implementation timeline."

Acorda said it is disappointed in the court's decision and is planning its appeal. "We believe that we demonstrated novel and unexpected findings in our Ampyra development program that led to the issuance of valid patents," Cohen said in a statement.

The company said it has developed contingency plans to address its business needs and objectives in the event of a loss of Ampyra exclusivity and will provide an update after finalizing the implementation timeline.

Ampyra net revenue in the US was $492.8m in 2016. Biogen markets the drug as *Fampyra* outside the US. The company's total net revenues for the year were $519.6m.

Leerink analysts said in a March 31 note that Acorda reported at the Leerink Global Healthcare Conference in February that in the event of a negative Ampyra legal decision, its first and second priorities would be its CVT-301 (inhaled L-Dopa) for Parkinson's disease in off episodes and tozadenant, an adenosine A2a receptor antagonist in Phase III trials as an adjunctive treatment to levodopa in PD patients. The analysts said CVT-301 looks poised for approval in 2018 given its positive Phase III data and clean long-term safety. They said they view the tozadenant pivotal program as a "'coin flip' given solid Phase II data counterbalanced by mixed/negative results for other products with a similar mechanism."

In an April 3 note, Aegis Capital Corp analyst Robert LeBoyer suggested that Acorda has a good case to make in its appeal. He said he disagreed with the district court's conclusion that early studies of dalfampridine provided enough information for a reasonable expectation of success.

"The court seemed to view the prior art studies as more predictive of successful outcome than we believe the data justify. Industry-wide databases show that each phase of clinical development has a high rate of failure and only a small percentage successfully reach the marketplace," he said.

DIFFERENT PRIOR ART IN IPR CASE

Bass took a different approach than the generic manufacturers in challenging the four Ampyra method of use patents at issue in the district court litigation. Bass' Coalition for Affordable Drugs claimed that Acorda's S-1 registration statement – which a company files before going public – constitutes prior art because it was published more than one year before the earliest effective filing dates of the patents. *(Also see "Patent Challenges Via IPR Still Pretty Scary, Even After Acorda's Win" - Pink Sheet, 25 Aug, 2015.)*

On March 9, the US Patent and Trademark Office's Patent Trial and Appeal Board (PTAB) upheld all four patents, the latest of which expires in May 2027. *(Also see "Acorda Defeats Kyle Bass, Now Awaits Ruling In Ampyra ANDA Litigation" - Pink Sheet, 9 Mar, 2017.)*

The IPR process is considered more favorable to patent challengers than district court litigation since it has a lower burden of proof and a broader standard for deter-

mining the meaning of patent claim terms. And in other cases, patent owners have prevailed in district court only to lose in PTAB proceedings. That was **Novartis AG**'s experience with its *Exelon* (rivastigmine) patch. The US Court of Appeals for the Federal Circuit affirmed a district court ruling on the validity of two Exelon patents, but PTAB subsequently found them to be unpatentable. *(Also see "New Patent Battleground: Inter Partes Reviews Besiege Innovators" - In Vivo, 14 Dec, 2015.)*

WANING HEDGE FUND INTEREST IN PTAB

Bass, founder of Hayman Capital Management, jumped into the IPR arena in January 2015, announcing he would be filing petitions against drug companies and betting that their share price would fall. He filed 34 IPR petitions against 10 companies. PTAB instituted review of 20 and declined review of 14. Bass has scored a victory in 50% of cases. Of the 19 final written decisions the board has issued, 10 have been in Bass' favor (*see chart below*).

While Bass' foray into challenging patents caused an uproar in industry, the outcomes of the cases are similar to those filed by other parties.

"Each of these cases, by Bass or others, are very fact driven by the time you get to a final written decision," Knobbe Martens partner Kerry Taylor said.

As for whether these cases pose a risk to the pharmaceutical industry going forward, Taylor said investment-related petitions don't seem to be as popular now as they were when Bass initiated them. "It appears to be a diminishing risk, at least from the investment community," he stated.

Bass himself seems to have dropped his interest in the endeavor. He has not filed a petition since 2015. All but one of them have been decided. The PTAB heard oral arguments in the remaining case, in which the Coalition is challenging Fresnius Kabi USA's *Diprivan* (propofol) patent claims, on March 13.

In the most recent final written decision issued on March 21, PTAB upheld the validity of patents on **Biogen Inc.**'s multiple sclerosis drug *Tecfidera* (dimethyl fumarate). Biogen also won a patent interference proceeding against **Forward Pharma AS**. In a March 31 decision, PTAB ruled that the claims in Forward's patent application that cover a method of treating MS with a 480 mg per day dose of dimethyl fumarate are unpatentable due to a lack of adequate written description.

Forward said it believes the claims in its application are patentable and that it is entitled to priority over Biogen and that it would appeal to the Federal Circuit. Forward announced in January that it had entered into a settlement and license agreement with Biogen. Forward said that on Feb. 9 it received a non-refundable cash fee of $1.25bn from Biogen in connection with the agreement and that if it is successful on appeal it anticipates Biogen would have to pay future royalties of 10% on US net sales of Biogen products, including Tecfidera, indicated for treating MS until the expiration or invalidation of its patents.

Published online April 3, 2017

Kyle Bass' IPR Batting Stats

Kyle Bass' group, the Coalition for Affordable Drugs, filed 34 inter partes review petitions (two were filed under his name or that of coalition co-founder Eric Spandgenberg). PTAB declined to institute review of 14 petitions and instituted review of 20. Below are the outcomes of the 20 cases, one of which has yet to be decided.

PATENT OWNER/DRUG	CASES	FINAL WRITTEN DECISION
Acorda Therapeutics Inc.	IPR2015-01850	Bass loses challenges
Cosmo Technologies Ltd.	IPR2015-00988	Bass loses challenge
NPS Pharmaceuticals Inc.	IPR2015-00990	Bass wins challenges
Biogen International GmbH	IPR2015-01993	Bass loses challenge
Celgene Corp.	IPR2015-01092	Bass wins challenges
Pozen Inc.	IPR2015-01718	Bass loses challenge
Anacor Pharmaceuticals	IPR2015-01776	Bass wins challenges
The Trustees of the University of Pennsylvania	IPR2015-01835	Bass loses challenges
Fresenius Kabi USA LLC	IPR2015-00254	Pending; oral arguments held on March 13
Alpex Pharma	IPR2015-00245	Bass wins challenge; patent owner declined to contest the issues and patent claims were canceled

Before Price Controversy, Emflaza Got Easy US Nod With Old But Good Enough Data

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The US FDA's approval of **Marathon Pharmaceuticals LLC**'s *Emflaza* (deflazacort) for Duchenne muscular dystrophy quickly set off a controversy about orphan drug pricing and value, but agency review documents show that the decision about the drug's efficacy and safety was anything but controversial.

"The benefits of deflazacort plainly outweigh its risks," Office of Drug Evaluation I Deputy Director Robert Temple concluded in his Emflaza review memo. "Beneficial effects have been shown on the muscle weakness (and its consequences) that is the principal early health consequence of DMD, and deflazacort has the expected risks of any chronically used corticosteroid."

Emflaza took less than three years from IND to NDA approval, with a smooth and efficient FDA review that stands in marked contrast to the contentious experience of the first therapy for DMD, **Sarepta Therapeutics Inc.**'s recently approved exon-skipping oligonucleotide *Exondys 51* (eteplirsen).

The consistency of deflazacort's effect on clinically meaningful endpoints, primary and secondary, helped the Emflaza NDAs overcome the limitations of the 20-year-old clinical trial data supporting the DMD applications. FDA approved tablet and oral suspension formulations of the corticosteroid on Feb. 9. (*See table for a timeline of Emflaza's development and review.*)

"There has been great interest in genetic interventions that could increase the amounts of functioning dystrophin," Temple said, referencing Exondys, "but since the 1990's corticosteroids have been used in DMD and have become the standard of care."

Both the Exondys and Emflaza approvals demanded considerable regulatory flexibility from FDA, and both received orphan drug incentives and expedited reviews as the first treatments for a serious unmet medical need. Exondys received accelerated approval on the basis of what Temple called a "small increase in muscle dystrophin." Exondys reviewers did not find improvement in clinical endpoints and questioned the reliability of the biomarker findings. *(Also see "Exondys Approval: Measured Efficacy Outcomes Vs. Patient 'Anecdotes'" - Pink Sheet, 28 Dec, 2016.)*

Emflaza required a different kind of flexibility from the agency. Deflazacort has been marketed overseas since the 1970s, as **Sanofi**'s *Calcort* and generics, although Emflaza is the first time it has been submitted in the US. Deflazacort became a standard frontline treatment for Duchenne muscular dystrophy despite never having been approved for the indication anywhere. FDA reviewed the application under the 505(b)(2) NDA pathway, allowing reviewers to rely on external data.

DMD patients had been importing deflazacort at a cost of around $1,000 a year, and when Marathon announced a price in excess of $80,000 for Emflaza controversy erupted. Marathon paused the launch of deflazacort, and then sold the product to **PTC Therapeutics Inc.** *(Also see "PTC Gambles On Success With Emflaza; Says Price Revision Is Needed" - Scrip, 16 Mar, 2017.)*

The furor has drawn attention to two regulatory incentive programs in particular: orphan drug designation and rare pediatric disease priority review vouchers. *(Also see "Sponsors May Race For Rare Pediatric Voucher Designations As Deadline Nears" - Pink Sheet, 22 Dec, 2016.)*

Sen. Bernie Sanders (I-VT) and Rep. Elijah Cummings (D-MD) have used the Emflaza price as the launching pad for a series of letters to FDA demanding details of the DMD drug's review. *(Also see "Marathon's High-Priced Window May Not Stay Open Long" - Scrip, 13 Feb, 2017.)*

"We believe Marathon is abusing our nation's 'orphan drug' program, which grants companies seven years of market exclusivity to encourage research into new treatments for rare diseases – not to provide companies like Marathon with lucrative market exclusivity rights for drugs that have been available for decades," the legisla-

> Deflazacort has been marketed overseas since the 1970s and became a standard frontline treatment for Duchenne muscular dystrophy despite never having been approved for the indication anywhere.

tors asserted in their original Feb. 13 letter. A March 15 letter focuses on the "limited amount of innovative research the company appears to have conducted to develop Emflaza" and asks for review details and precedents. On March 22, they sent a letter to new Emflaza owner PTC Therapeutics urging pricing restraint.

Were it not for the PR debacle surrounding the price, Emflaza could have been held up as one kind of model for orphan drugs. The review shows how FDA chooses not to fetishize innovation, but also applies regulatory flexibility to the project of improving oversight and access to orphan products otherwise available on the "gray market" of personal importation, pharmacy compounding, and investigator-sponsored treatment protocols.

CDER Director Janet Woodcock defended the use of orphan drug incentives for non-novel products in a recent podcast interview, pointing out that "if the drugs aren't studied for rare diseases, then people with rare diseases are treated off label with a variety of drugs, where you don't have information about whether they work and what their safety is, and they aren't often reimbursed." *(Also see "Orphan Drug Act: Congressional, FDA, NORD Reviews Come Amid Pricing Debate" - Pink Sheet, 7 Mar, 2017.)*

Official FDA approval also ensures that product quality and manufacturing conform to US standards, which is not necessarily the case when patients must personally import products like generic deflazacort from overseas. And FDA's authority to require post-marketing studies of safety issues means that nagging questions, like the characterization of deflazacort metabolites and elucidation of the drug's cardiac effects, will be addressed in a systematic fashion.

MAKING DO WITH IMPERFECT INFORMATION

The Emflaza review team's evaluation of the imperfect deflazacort clinical data is a good illustration of the regulatory flexibility that has been one hallmark of the Center for Drug Evaluation and Research under the leadership of Woodcock and recently retired Office of New Drugs Director John Jenkins. Reviewers regularly turn to the totality of the evidence when faced with problematic datasets with products for serious unmet needs. *(Also see "How To Save A Drug: Iressa's Return Relied On Consistency Across Totality Of Evidence" - Pink Sheet, 26 Oct, 2016.)*

Marathon acquired rights to two older studies of Emflaza in DMD to serve as the efficacy data for the NDAs. The linchpin was Study NM-001, a randomized, placebo-controlled trial that enrolled 196 male patients aged 5 to 15 years old in the US and Canada. Nor-

Emflaza Clinical Development Timeline

IND #119258	
8/16/2013	Orphan drug designation granted
11/21/2013	Pre-IND meeting
10/2014	IND submitted
11/21/2014	Fast track status granted
3/2/2015	Rare pediatric disease designation requested
8/10/2015	Rare pediatric disease designation granted
8/4/2015	Pre-NDA meeting; Marathon proposes submitting NDA with data from early 1990s trials using Sanofi's *Calcort* brand of deflazacort
9/18/2015	Tradename Emflaza deemed conditionally acceptable by DMEPA
NDA #208684 (ORAL TABLET) AND #208685 (ORAL SUSPENSION)	
6/9/2016	NDAs submitted as 505(b)(1) applications
10/26/2016	Mid-Cycle communication
11/10/2016	FDA email informs Marathon that the NDAs will be reviewed under the 505(b)(2) pathway
12/13/2016	Late-Cycle meeting
2/9/2017	Approved on PDUFA goal date
2/13/2017	Marathon "pauses" launch amid controversy over price
3/16/2017	PTC Therapeutics announces purchase of all rights to Emflaza

dic Merell-Dow, which would become part of what is now Sanofi, conducted NM-001 between 1993 and 1995. An Italian study in 29 children from 1988-1991, known as NM-002, provided supportive evidence of efficacy.

Missing documentation hampered FDA's ability to conduct its normal thorough examination of the clinical efficacy data. With NM-001, for example, "as responsibility for the study passed from the original sponsor to some of the study investigators and then to the current applicant, study materials such as completed case report forms and other data became unavailable," review team leader Nicholas Kozauer noted. FDA could not conduct clinical study site inspections because "only three of the nine clinical sites … had sufficient information allowing subjects to be matched with the respective site."

Financial due diligence was also stymied. "When Marathon licensed the exclusive US rights to these studies in 2014, multiple attempts were made to contact all of the investigators to obtain financial information with respect to Marathon," Kozauer said. "Due to the amount of time that passed between when these studies were conducted and when Marathon licensed the rights, Marathon was either unable to make contact or solicit a response to the request for financial information for many of the investigators."

FDA's nonclinical reviewers were also challenged by the age of the efficacy studies. "No pharmacokinetic (PK) information was collected in those trials," Kozauer observed. Additionally, "direct bridging" of the clinical trial product to the to-be-marketed formulation (Emflaza) "was not feasible."

Faced with these limitations, FDA's clinical pharmacology review team undertook "a detailed consideration of the totality of the evidence provided in this application that would support the establishment of an indirect bridge between Emflaza and the formulation use in the clinical efficacy trials," Kozauer said. FDA was comfortable using the "totality of the evidence" in pharmacology because "the intrinsic properties of deflazacort are sufficient to ensure absorption regardless of pH and formulation changes," he noted. "Emflaza is unlikely to have lower bioavailability than the clinical formulation used in the efficacy trials."

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Emflaza's 505(b)(2) Pathway Review: Rare, But With Precedent

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Marathon did conduct a "limited battery of nonclinical studies" in support of the NDA, supervisory pharmacology reviewer Lois Freed said, including in vitro metabolism studies and toxicity studies in animals. This data resulted in the only recommendation against approval of Emflaza, from primary pharmacology reviewer David Hawver. (*See table for a listing of the Emflaza review team.*)

Hawver "concluded that the studies conducted by the sponsor, although consistent with the Division's recommendations provided during clinical development, are not adequate to support approval, from a nonclinical standpoint, because of the lack of safety data for two major metabolites," Freed summarized. The review team leader and division and office leadership agreed with her that the data could be acquired with a post-marketing requirement.

CONSISTENT SIGNALS OF EFFICACY

To assess the clinical utility of deflazacort, FDA looked for consistent signals of the drug's effect across the totality of the imperfect dataset. "The consistency of the findings across studies NM-001 and NM-002 argues for the plausibility of the observed effects representing a benefit attributable to deflazacort," clinical reviewer Rainer Paine concluded.

Study NM-001 showed a "small but statistically significant effect" for its primary muscle strength endpoint, Paine reported. "The overall results of the secondary endpoints provide support for the clinical relevance."

In total, "evidence from clinical trials indicates that deflazacort improves the muscle strength of DMD patients, slows the loss of strength over time, and improves the ability to accomplish tasks related to activities of daily living such as standing up, walking, and climbing stairs," Paine concluded.

NM-001's primary endpoint measured change from baseline in a measure of muscle strength after 12 weeks. (While the study ran for 52 weeks, placebo comparison was only possible for the first 12 weeks; all patients later received deflazacort or prednisone.) Both doses of deflazacort tested showed a "highly statistically significant" benefit at 12 weeks, Kozauer said, but "the size of the treatment effect on the modified MRC scale is small, approximately 1/4 to 1/3 of a point on the 11-point scale."

"Despite these relatively small effects versus placebo at Week 12, the fact that scores on this measure continue to show some improvement over 52 weeks of treatment, as opposed to the expected decline, is further supportive evidence that the effects observed at Week 12 are real and are likely to become more meaningful over time," Kozauer concluded.

FDA's efficacy conclusion was also informed by secondary endpoints using timed function tests that measured the time required for set actions, like time to stand from a supine position and time to walk 30 feet. "Although there is some inconsistency in the results of these additional endpoints, I find that the demonstration of highly statistically significant effects on three of the four timed function tests that were evaluated during the trial is additionally supportive

Emflaza Reviewers

DISCIPLINE	REVIEWER
Clinical	Rainer Paine
Statistics	Xiang Ling
Pharmacology/Toxicology	David Hawver
Clinical Pharmacology	Bilal AbuAsal
Quality	Martha Heimann
Study Integrity & Surveillance	Hasan Irier
Cross-Discipline Team Leader	Nicholas Kozauer
Regulatory Project Manager	Laurie Kelley

While the submitted data left open some questions about deflazacort's effect on QT interval, FDA felt the issue could be addressed post-marketing.

of a treatment benefit," Kozauer said.

"The consistency of the findings" on the timed function measures at 12 weeks "argues for the plausibility of the observed effects representing a benefit attributable to deflazacort," Paine said.

The small supportive efficacy trial submitted to the NDA, the Italian study NM-002, found similarly consistent effects even though interpretation of the trial's results "is substantially handicapped by its design," Kozauer observed.

NM-002's primary endpoint was change in muscle strength from baseline to year two. The study, however, dropped patients when they could no longer walk, and "the 2-year evaluation was rendered uninterpretable by loss of almost all placebo patients by 2 years because of loss of ambulation," Temple pointed out. FDA statistical reviewer Xiang Ling analyzed the data using the last available observation and found "a significant effect on preservation of muscle strength." The six month and one year data, "when most patients were still in the study, also showed a significant effect," he noted.

While the secondary endpoints in NM-001 and the whole NM-002 trial were critical to supporting FDA's conclusion that deflazacort demonstrated a clinically meaningful effect in DMD patients, the data's limitations prevent the findings from being included in labeling for Emflaza. FDA revised the clinical studies section of Marathon's proposed labeling "to primarily present the results of the analysis of the primary endpoint from Study NM-001, as this is the only positive finding that was statistically controlled for multiple comparisons," Kozauer said. "The overall support for this finding from the additional endpoints in Study NM-001, and Study NM-002, will only be briefly presented descriptively at a high level."

LOOKING OUTSIDE

Deflazacort's long-time availability in overseas markets proved a liability when the Emflaza pricing controversy hit, but that experience was a help in the assessment of the NDAs.

Kozauer found it "important to note the fact corticosteroids are considered standard of care for the treatment of DMD worldwide."

"While anecdotal clinical practice explicitly cannot serve as evidence in support of an approval, the broad experience with these agents in the treatment of DMD does at least provide an additional lens with which to view the efficacy data provided in the current application," Kozauer said.

While the submitted data left open some questions about deflazacort's effect on QT interval, FDA felt the issue could be addressed post-marketing in part because of the European marketing experience. The European summary of product characteristics for Sanofi's Calcort "does not list any cardiac adverse events related to arrhythmias or prolonged QT," the QT review pointed out.

Published online March 31, 2017

NEW PRODUCTS

FDA's NDA And BLA Approvals: Austedo

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

SPONSOR	PRODUCT	INDICATION	CODE	APPROVAL DATE
New Drugs				
Teva	Austedo (deutetrabenazine)	Treatment of chorea associated with Huntington's disease	S, 1	4/3/2017

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

What's Next For Antacid/Analgesic OTCs After Negative US FDA Panel?

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An FDA advisory panel acknowledged that nonprescription antacid/analgesic products are popular with consumers to relieve pain and upset stomach after consumption of too much food, alcohol or both, but is recommending that the formulations do not meet FDA's OTC monograph threshold for safe and effective ingredient combinations.

More broadly, the joint meeting of the Nonprescription Drug and the Drug Safety and Risk Management advisory committees on April 4 in Silver Spring, Md., also generated recognition from medical and research experts for FDA's position that the monograph process has become unviable and, in addition to impeding the introduction of additional ingredients and indications, prevents the agency from efficiently responding to problems with monograph products on the market.

The joint panel voted 15-5, with no abstentions, that combining antacid with aspirin, acetaminophen or other analgesic ingredients should not be allowed under an OTC monograph.

The recommendation, and the panel's wide-ranging discussion, gives FDA additional information to consider as it evaluates whether formulation, labeling or other changes are needed for the products due to concerns about a risk of serious internal bleeding potentially linked to aspirin, the analgesic used in many of the products. A spokeswoman said the Division of Nonprescription Drug Products in the Center for Drug Evaluation and Research has not set a timetable for its next step in evaluating the products' safety and determining whether a regulatory action is needed.

The most well-known antacid/analgesic combination, the *Alka-Seltzer* line of original, lemon-lime and extra strength products, is being reformulated without aspirin due to consumer preferences and to eliminate potential harm from misuse of the products, said the manufacturer, **Bayer AG**'s US consumer business, in advance of the FDA advisory panel meeting. *(Also see "US FDA Serves One Antacid/Analgesic Question For AdComm, Opens Tap On Hangover Discussion" - Pink Sheet, 31 Mar, 2017.)*

FDA announced in June 2016 that it would seek advisory committee review of whether a risk of serious bleeding linked to use of OTC antacid/aspirin products should spur further agency action than a label warning already required for the products. Antacid/aspirin products are among the OTCs containing acetaminophen or NSAIDs that were required to add a label warning on a risk of serious bleeding in a 2009 rule that went beyond changes the agency proposed in a 2006 tentative final rule to amend the monograph for internal analgesics, antipyretics and antirheumatics. *(Also see "OTC Antacid/Aspirin Bleeding Risk Raises Concerns At CDER" - Pink Sheet, 13 Jun, 2016.)*

COMBINATIONS USED FOR SINGLE INDICATION

Most panel members voting in the majority noted the products' utility for consumers while also saying they are concerned about the risk of serious internal bleeding; they are not convinced that antacid/analgesic combinations are effective; and they consider single-ingredient antacids for upset stomach symptoms or analgesics for minor head or body aches are a safer option.

Physicians and medical researchers on the panel pointed out that consumers are likely to use antacid/analgesic combinations when they have either an upset stomach or minor aches following overindulgence, not both. Through such unintentional misuse, a consumer ingests unneeded analgesics, potentially contributing to internal bleeding or to liver damage; or adds unnecessary sodium from the ingredients intended to treat upset stomach.

Neil Farber, a professor of clinical medicine at the University of California, San Diego, raised particularly numerous concerns and questions about allowing antacid/analgesic combinations to remain available under a monograph. Farber, a general internist, noted consumers' unintentional misuse of the products among his concerns.

He noted some studies show aspirin limits the efficacy of antacids. "From that perspective, at least as aspirin is concerned, that in itself indicates that this is not an acceptable drug."

"There is some risk including patient misunderstanding as well as the fact that there remains some question about efficacy," Farber added after casting his vote.

ADVISORY COMMITTEES' VOTE

"Is the combination of an analgesic with antacids a rational combination for OTC use for the relief of minor aches and pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea?" **N - 15; Y - 5**

NDAC member Janet Engle, a professor and head of the pharmacy department at the University of Illinois in Chicago, also noted the risk factor of consumers misunderstanding labels.

"Maybe we have to recommend two products" when consumers have acid indigestion and minor pain, Engle said. "To me [antacid/analgesic combinations] are not good solutions for our patients," she added.

COMBINING INGREDIENTS RATIONAL?

While the discussion focused on the products' safety and efficacy, the panel's vote, as stated in FDA's agenda for the meeting, was on the question of whether the combination of an analgesic with antacids is "a rational combination for OTC use for the relief of minor aches and pains associated with heartburn, sour stomach, acid indigestion, fullness, belching, gas, or nausea?"

"To me, I do not see this as a rational combination because I would not treat upset stomach with an aspirin product," said panel Chairwoman Christianne Roumie, an internal medicine and public health professor at Vanderbilt University and a physician at the Veterans Affairs Tennessee Valley Healthcare System.

FDA's regulation for the monograph process does not define rational, but uses the term to indicate that a combination of ingredients would be considered safe and effective for an indication and without either ingredient diminishing the effectiveness of the other.

The regulatory language on the monograph threshold for ingredient combinations also states, "when used under adequate directions for use and warnings against unsafe use, provides a rational concurrent therapy for a significant portion of the target population."

Panel members voting to recommend that antacid/analgesic combinations should remain available under a monograph emphasized that data FDA presented did not indicate a significant safety problem.

"I don't hear anything that says they're not safe and if people are buying them they must consider them effective," said Timothy Lipman, a clinical medicine professor at Georgetown University and former head of GI-hepatology-nutrition section at the Washington VA Medical Center.

"I think this combination is not rational but I'm not going to vote against" keeping antacid/analgesic combinations on the monograph without stronger data suggesting a safety problem, Lipman added.

The Consumer Healthcare Products Association aligned with panel members unconvinced by the agency's data. CHPA, represented at the meeting by staff and by consultants making a presentation on the hangover monograph indication, said later in a statement that the "advisory committees ultimately took a nonbinding vote questioning the combination of analgesic and antacid ingredients, but data presented by FDA and other experts showed that the reported rate of serious adverse events of bleeding over the past 40 years for such combinations is extremely rare."

In the event that FDA changes the monograph and no longer allows marketing antacid/analgesic combinations as monograph products, drug firms could submit new drug applications to the agency and conduct clinical trials to show their safety and efficacy.

From the editors of The Tan Sheet. Published online April 4, 2017

UNCHANGED LABELING MAY BE UNSAFE

Thomas Smith, an attorney and associate dean of assessment and administration at Manchester University College of Pharmacy in Fort Wayne, Ind., made perhaps the strongest points both for the potential safety risks with antacid/analgesic combinations and for how the monograph process prevents FDA from acting quickly to resolve a potential safety problem.

Although imposing label changes on monograph products requires a rulemaking, Smith pointed out that, nevertheless, current approved labeling initially should "encompass patient understanding and being able to use that drug in a safe way."

However, CDER officials have made clear that for some monograph products, formulations or indications allowed when the process began in the early 1970s may no longer be supported by science. Still, while manufacturers and marketers have voluntarily made changes to monograph product labeling or formulations, FDA does not expect it could force prompt action if needed. *(Also see "Safety Review For Upset Stomach, Hangover OTCs Reconsiders Science" - Pink Sheet, 7 Mar, 2017.)*

Karen Mahoney, deputy director of FDA's OTC drugs office, in separate remarks to the panel during the course of the meeting, explained that "we have big challenge in our ability to change a monograph," a process that "can take years."

The tentative final monograph that allows marketing antacid/analgesic combinations for relief of minor pain and upset stomach caused by overindulgence, Mahoney said, was "made a long time ago and science has progressed considerably."

Smith, who voted to allow antacid/analgesic combinations to remain available, said that given FDA's monograph process and the potential for harm from misuse of some OTC ingredients, "It just seems to me that because of this challenge, there are products on the market that are not labeled with adequate directions for safe use."

"The answer would be, probably, yes," Mahoney said.

'Evolving' With Health Care, CHPA Considers Device, Supplement Sectors

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The Consumer Healthcare Products Association is conducting an "inward analysis" on potentially expanding membership opportunities to firms in additional product categories where current members increasingly are extending their businesses.

"Health care, especially consumer health care, is evolving at lightning speed, and so too, must CHPA," said President and CEO Scott Melville at the trade group's Annual Executive Conference in Amelia Island, Fla., on March 21.

CHPA's 2020 project will analyze how the association can better "evolve with members," includes "taking a fresh look at membership, or at least categories of membership," and will consider ways to "more actively" engage these areas, specifically the dietary supplement industry, said Melville.

"Project 2020 will provide a road map for the future," Melville said.

He said the analysis would consider implications of expanding membership to more companies that market supplement products beyond the current 26 members that manufacture or market vitamins, supplements or nutritionals in addition to OTC drugs, including **Pfizer Inc.**, **Procter & Gamble Co.**, Prestige Brand Holdings Inc. and **Perrigo Co. PLC**.

CHPA says 35% of its members market products in the supplement category while 94% market products that include OTC drug ingredients.

Melville also suggested membership could expand to firms marketing consumer medical devices, those categorized by FDA as class I and II.

Class I devices present "minimal potential for harm to the user" and include products such as elastic bandages and enema kits, while class II comprise "most" medical devices such as pregnancy kits, according to FDA. CHPA notes fitness trackers and other wearable devices that aid in health maintenance can also fit this category.

Melville also observed that the supplement and consumer device categories have similarities with nonprescription drugs. "These products categories have important regulatory distinctions from OTC drugs, but also much in common. First and foremost, they are all consumer health care products, are all regulated by the FDA, are not covered by insurance and don't require medical professionals' intervention, and are purchased at retail by the consumer."

CHPA chief Scott Melville: health care "is evolving at light speed."

Consumer health care market researchers point to more consumers embracing self-care for minor ailments and looking for ways to treat more conditions without using health care serves, often by using OTC drugs and supplements. OTC firms, however, have been slow to offer digital technology tools to guide consumers to products that facilitate their self-care interests. *(Also see "Technology Gap Separates OTC Drug Firms From Self-Care Sales Growth" - Pink Sheet, 16 Mar, 2017.)*

CHPA spokesman Mike Tringale emphasized the 2020 project is in its infancy as an effort to consider "broadening our scope in the way our members have." He added the group's focus of remains on its existing members, businesses that manufacture, market or distribute consumer health products.

CHPA also has associate members that supply goods and services to manufacturers, including advertising agencies, television networks, contract manufacturers, internet services, law firms, market researchers and packaging companies.

The group already works with the Council for Responsible Nutrition and the Personal Care Products Council on joint

7 MEMBERS NEW TO BOARD

During the March 19-22 conference, CHPA also elected members and officers to its board. One-third of the board is elected annually, with manufacturers elected for three years and associate members for two. In addition to 16 members re-elected to board, seven new members were elected:

- Agustin Caceres, president, **North America, Genomma Lab USA Inc.**
- Peter Caldini, regional president, **North America, Pfizer Consumer Healthcare**
- Sharon Glass, senior VP, brand development, **Catalina**
- Avani Kanubaddi, CEO, **Welmedix Consumer Healthcare**
- Mike Rosenberg, senior VP, national advertising, **Healthgrades Inc.**
- Rich Simonson, chief operating officer, **Carma Laboratories Inc.**
- Jeffrey Vernimb, general manager, **Moberg Pharma North America LLC**

research and policy statements on topics that overlap the OTC space and the industries those trade groups represent.

During his presentation, Melville also touched on the group's priorities in 2017, including anticipating the introduction of a bill to modernize FDA's OTC monograph system and establish a user fee program to pay for the agency's work, and backing legislation to again allow direct purchases of OTC drugs with pre-tax savings accounts. *(Also see "OTC Monograph Reform, User Fee Legislation Coming 'Any Day' – CHPA" - Pink Sheet, 30 Mar, 2017.)*

Another point in his presentation was on concern about state legislation introduced in Hawaii to ban the use of oxybenzone-containing sunscreens. *(Also see "Hawaii's Proposed Oxybenzone Sunscreen Ban Fails Science Test – CHPA" - Pink Sheet, 27 Mar, 2017.)*

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Novel Biologics In US Might Not Start Getting Suffixes Until August

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In January, the US FDA finalized a guidance that changes the way biologic products should be named. So far, the agency hasn't been following it.

Over the course of a week last month, FDA approved three novel biologics – **Genentech Inc.**'s multiple sclerosis treatment *Ocrevus* (ocrelizumab), **Sanofi** and **Regeneron Pharmaceuticals Inc.**'s atopic dermatitis treatment *Dupixent* (dupilumab), and **Pfizer Inc.** and **EMD Serono Inc.**'s metastatic Merkel cell carcinoma treatment *Bavencio* (avelumab) – all without the four-letter suffix, even though that's has been agency's recommended practice since the guidance on nonproprietary naming was finalized on Jan. 12. *(Also see "Biologic Product Naming: US FDA Sticks With Suffixes 'Devoid Of Meaning'" - Pink Sheet, 12 Jan, 2017.)*

Asked about this discrepancy regarding the approval of Bavencio on March 23, the agency told the Pink Sheet that "FDA issued the final guidance at a point in our review of the application that did not allow sufficient time for FDA to designate a proper name that includes a suffix as described in the guidance."

"In order to avoid delaying the approval of Bavencio and in the interest of public health, FDA licensed the biological product with a designated proper name that did not include a suffix," the spokeswoman added. "We intend to work with the application holder for this biological product to implement the naming convention described in the guidance."

The agency gave a nearly identical response five weeks earlier regarding the Feb. 15 approval of **Valeant Pharmaceuticals International Inc.**'s psoriasis treatment *Siliq* (brodalumab), which was the first novel biologic approved since the guidance was finalized. *(Also see "Where's The Suffix? Valeant's Siliq Approved Without Four-Letter Identifier" - Pink Sheet, 16 Feb, 2017.)*

EARLY SUBMISSIONS REQUESTED

FDA could not comment on at what point in the application process it would consider to be too late for sponsors to submit their proposed suffixes to have their product approved with the suffix immediately attatched.

The guidance, however, notes that applicants should make their submissions during the investigational new drug application (IND) phase or at the time of a biologics license application (BLA) submission.

Therefore, FDA might not be planning on approving a biologic with a four-letter suffix unless the proposed suffixes are submitted along with the BLA, in order to prevent review delays. Consequently, BLAs submitted before the guidance was finalized likely won't see approval with a suffix attached at that time. As the agency has indicated, it will work with sponsors to implement suffixes after the approval has been announced.

So it may not be until August over even later when the US FDA finally approves a biologic with an arbitrary four-letter suffix attached to the nonproprietary name. **Dynavax Technologies Corp.**'s hepatitis B vaccine *Heplisav-B* (rHBsAg-1018 ISS) appears have the earliest user fee date of the applications submitted after the guidance was finalized.

Heplisav was submitted to FDA in February 2017, and has user fee date of Aug.10. The company did not respond to inquiries about

whether it had submitted suffixes to FDA as part of the application.

Suffixes seem even further away for biologics whose applications were submitted before the guidance was finalized. A **CSL Behring** spokeswoman tells the Pink Sheet that it has not yet been asked for, nor have it volunteered a four-digit suffix for a market application. The company has applications pending at FDA, including for *CSL830* (C1 esterase inhibitor, human) and *Privigen* (immune globulin intravenous).

> The agency's two-track approach makes for a confusing situation, given that the guidance expressed concerns about adverse patient perceptions if FDA only applies the naming convention to biosimilars, and not originator products.

A **Janssen Inc.** spokeswoman tells the Pink Sheet that it is currently developing a strategy to comply with the guidance. Janssen currently has BLAs and sBLAs pending for several products (*see table*).

A CONFUSING PORTRAYAL OF PRIORITIES

It appears attaching the suffixes to novel biologics has not been a huge priority for FDA. Of the products approved with suffixes so far, all four are biosimilars: **Sandoz Inc.**'s *Zarxio* (filgrastim-sndz), Pfizer's *Inflectra* (infliximab-dyyb), Sandoz's *Erelzi* (etanercept-szzs) and Amgen's *Amjevita* (adalimumab-atto).

Zarxio was approved with a suffix before the draft guidance was even issued in August 2015; the other three were approved with suffixes before the guidance was finalized. Zarxio's suffix will likely change, since FDA now prefers a random assortment of letters, rather than a series that identifies the sponsor or anything else.

The agency's two-track approach makes for a confusing situation, given that the guidance expressed concerns about adverse patient perceptions if FDA only apply the naming convention to biosimilars, and not originator products. "Such an approach could be misinterpreted as indicating that biosimilar products differ from their reference products in a clinically meaningful way or are inferior to their reference products for their approved conditions of use," FDA says in the guidance.

"The inclusion of an FDA-designated suffix in the nonproprietary name of biological products licensed under section 351(a) or 351(k) of the PHS Act should have the added benefit of helping to avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway," the guidance adds.

The agency has also expressed concerns about health providers confusing products as more biological medicines become approved, which could lead to inadvertent substitution and medication errors. There are currently 77 biologics approved by FDA that share 25 nonproprietary names.

"FDA believes the nonproprietary naming convention for originator biological products, related biological products, or biosimilar products should help prevent inadvertent substitution," the guidance states. "Inadvertent substitution may lead to unintended alternating or switching of biological products that are not determined by FDA to be interchangeable with each other. This naming convention should facilitate safe use and help to protect the safety of patients."

WHAT'S IN THE QUEUE?

In addition to Heplisav-B, there are at least two biologic applications pending at FDA which were received after the guidance was finalized, both seeking to expand the indications of approved products:

- **Amgen Inc.**'s *Blincyto* (blinatumomab), and
- **GlaxoSmithKline PLC**'s influenza vaccine *Fluarix Quadrivalent*.

Blincyto garnered accelerated approval in 2014 for the treatment of refractory B-cell recursor acute lymphoblastic leukemia, and is seeking to obtain full approval. Amgen announced it submitted its application Feb. 14. It has a user fee date of Dec. 14. Amgen declined to state whether it had submitted potential suffixes, offering instead a general comment on the guidance:

"As a developer of both innovative biologics and biosimilars, Amgen is pleased that the FDA has finalized guidance requiring a distinguishable suffix for all biologic medicines, including originator and biosimilar products. This is an important step as it will assist in the tracking of individual products back to the appropriate sponsor and reduce the potential for inappropriate or inadvertent switching of biologic medicines," the company states.

"However, Amgen believes that these goals would be best accomplished if the distinguishable nonproprietary name included a memorable suffix. This structure would foster effective safety monitoring of all approved biologics and support patient and physician confidence, promote manufacturer accountability and reliability of supply, and ultimately, play a key role in establishing a successful marketplace."

GSK is seeking to expanded population for its quadrivalent vaccine to include pediatric patients ages six months to 35 months. It announced the filing of the sBLA March 15, with a user fee date of Jan. 15, 2018. "GSK has no comment regarding the FDA guidance at this time," the company told the Pink Sheet. "Our submissions to the FDA regarding any potential naming for our investigational vaccines or prescription medicines are still under review and therefore confidential."

There are at least 23 other biologics – 14 novel biologics and nine supplemental biologics – that are pending with FDA and were submitted prior to the guidance being finalized. Given FDA's approach so far, those seem unlikely to be initially approved with suffixes.

But there are also at least seven biosimilars pending with FDA, and since biosimilars have all been approved with a suffix, those undoubtedly will as well – if indeed they are approved.

From the editors of the Tan Sheet. Published online April 6, 2017

Pending Biologic/Biosimilar Applications

PRODUCT	SPONSOR	DATE SUBMITTED	USER FEE DATE
SB2 (infliximab biosimilar)	Samsung Bioepis and Merck	March 2016	April 2017
Brineura (cerliponase alfa)	BioMarin	May 27, 2016	April 27, 2017
Tecentriq (atezolizumab) – sBLA	Genentech	October 2016	April 30, 2017
Actemra (tocilizumab) – sBLA	Genentech	November 2016	May 2017
Keytruda (pembrolizumab) – sBLA	Merck	November 2016,	May 10, 2017,
Nonacog beta pegol (Factor IX, recombinant, glycopegylated)	Novo Nordisk	May 16, 2016	May 16, 2017
Retacrit (epoetin alpha biosimilar)	Pfizer/Hospira	December 2016	June 2017
CSL830 (C1 esterase inhibitor, human)	CSL Behring	June 2016	June 2017
Subcutaneous rituximab and recombinant human hyaluronidase	Genentech and Halozyme	August or September 2016	June 26, 2017
CHS-1701 (pegfilgrastim biosimilar)	Coherus BioSciences	Aug. 9, 2016	June 9, 2017
Darzalex (daratumumab) – sBLA	Janssen Biotech, Genmab	Aug. 17, 2016	June 17, 2017
Soliris (eculizumab) – sBLA	Alexion Pharmaceuticals	Jan. 9, 2017	Oct. 23, 2017
Evenity (romosozumab)	Amgen and UCB	July 19, 2016	July 19, 2017
Subcutaneous Benlysta (belimumab)	GlaxoSmithKline	Sept. 23, 2016	July 9, 2017
Inotuzumab (ozogamicin)	Pfizer	December 2016	August 2017
Lucentis (ranibizumab) – sBLA	Genentech	October 2016	August 2017
Human anti-rabies immunoglobulin	Kamada and Kedrion	June 2016 to August 2016	Aug. 29, 2017
BI 695501 (adalimumab biosimilar)	Boehringer Ingelheim	November 2016	September 2017
Mylotarg (gemtuzumab ozogamicin)	Pfizer, UCB	November 2016	September 2017
MYL-1401O (trastuzumab biosimilar)	Mylan and Biocon	Nov. 8, 2016	Sept. 3, 2017
ABP 215 (bevacizumab biosimilar)	Amgen and Allergan	Nov. 15, 2016	September 14, 2017
Sirukumab	GlaxoSmithKline and Janssen Biotech	Sept. 23, 2016	Sept. 23, 2017
Stelara (ustekinumab) – sBLA	Janssen	December 2016	October 2017
Privigen (immune globulin intravenous, human, 10% liquid)	CSL Behring	December 2016	October 2017
Benralizumab	AstraZeneca	October 2016 to December 2016	October 2017 to December 2017
MYL-1401H (pegfilgrastim biosimilar)	Mylan and Biocon	Dec. 9, 2016	Oct. 9, 2017
Simponi Aria (golimumab) – sBLA	Janssen Biotech	Dec. 22, 2016	Oct. 22, 2017
Shingrix (herpes zoster vaccine)	GlaxoSmithKline	Oct. 24, 2016	Oct. 24, 2017
Guselkumab	Janssen	Nov. 17, 2016	Nov. 17, 2017
Blincyto (blinatumomab) – sBLA	Amgen	Feb. 14, 2017	Dec. 14, 2017
Heplisav-B (hepatitis B vaccine, rHBsAg-1018 ISS)	Dynavex	February 2017	Aug. 10, 2017
Bavencio (avelumab) – sBLA	Pfizer and Merck KGAA	September 2016	May 2017
Fluarix Quadrivalent (influenza vaccine)	GlaxoSmithKline	March 15, 2017	Jan. 15, 2018

'Critical' Issues Need Resolution Before ICH Q12 Proceeds To Next Step

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There are still some outstanding issues that need to be resolved before the International Conference on Harmonization's Q12 guidance advances to the next step, including consensus on established conditions and post-approval change management protocols. Yet there was agreement that there should be three categories for reporting post-approval changes.

Moheb Nasr, the ICH Q12 rapporteur, discussed progress being made by the Expert Working Group (EWG) on the seventh draft of the ICH Q12 guideline at a March 22 meeting of Product Quality Research Institute/FDA meeting in Rockville, Md.

Nasr also told Pink Sheet that there was agreement on three options for classifying post-approval changes. These are:

- **Prior approval:** for certain changes considered to have sufficient risk to require review and prior approval;
- **Notification:** for certain moderate to low risk changes which do not need prior approval. These changes are communicated with the regulatory authority as a formal notification that takes place in advance of, or within a defined period of time after implementation, according to regional requirements; and
- **Do and record:** this is for the lowest risk changes that are only managed and documented within the pharmaceutical quality system and not reported, but may be assessed on inspections.

The former version called for four categories for classifying post-approval changes *(Also see "ICH Q12 Experts Develop Four-Tier Scheme For Harmonizing Post-Approval Changes" - Pink Sheet, 8 Aug, 2016.)*.

Nasr, who is **GlaxoSmithKline PLC** CMC strategy VP, said that the EWG developing the guideline is a large team with diverse technical quality and regulatory expertise that is "committed to resolving the difficult technical and regulatory issues" posed by ICH Q12, and for this reason, the guideline has the potential to be "transformational."

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> The group developing the guideline is "committed to resolving the difficult technical and regulatory issues" posed by ICH Q12, and for this reason, the guideline has the potential to be "transformational."

Nasr said that while the ICH Q8, Q9, Q10 and Q11 guidelines use science- and risk-based approaches to assess changes over the lifecycle of products, the main emphasis of these guidelines was on the development side of the process, while ICH Q12 is meant to fill in the gaps by addressing post-approval changes.

Nasr said that the current version contains 11 chapters: an introduction, categorization of changes, established conditions, post-approval change management protocols, product specific lifecycle management, pharmaceutical quality system and change management, relationship between assessment and inspection, approaches to streamline changes to marketed products, a glossary, references and illustrative examples and case studies.

There is wide interest in ICH Q12; Nasr said that the EWG received over 2,500 comments on the draft guideline.

Nasr said that "the most important aspect of ICH Q12 is established conditions" and that "a well-developed and understood section on ECs will be critical to achieve alignment across the ICH regions and beyond."

ICH has incorporated the "established conditions" concept into Q12 that builds on FDA's guidance on established conditions released in May 2015. *(Also see "FDA Would Establish Conditions for Swift Manufacturing Changes" - Pink Sheet, 25 Jun, 2015.)* By defining such established

conditions, FDA's draft guidance clarifies which changes are so minor that companies should manage them within their internal pharmaceutical quality systems instead of seeking FDA approval for them or even reporting them to the agency. In recent years, more and more supporting information has crept into applications as manufacturers embraced the quality-by-design (QbD) paradigm that emerged in the mid-2000s.

Another important provision in ICH Q12 is post-approval change management protocols (PACMPs) which describe the changes a firm would like to implement during the lifecycle of a product along with the proposed reporting categories. Nasr said that the PACMP concept, although well-known, is not widely used.

A third important concept in the guideline is the product-specific lifecycle management (PSLCM) strategy, which serves as a central repository of the ECs, and provides a framework to facilitate and encourage a more strategic approach to lifecycle management.

Nasr said that there are still a number of critical issues and gaps to address before the guideline is approved. These include the following:

For established conditions, the EWG still must address:

- The need for a decision tree to identify and report ECs;
- The need to elaborate on a performance-based approach for defining established conditions; and
- The need for illustrative examples to show how the established concept can be used.

For product-specific lifecycle management strategy, the group must address:

- The need for benefits to be more clearly articulated;
- The need for illustrative examples; and
- The need to decide where to describe the strategy in the Common Technical Document.

For biotech products and vaccines, the group must address:

- The need for guidance to specify how Q12 could apply to these products.

Nasr said that the EWG is committed to reaching Step 1/2A at its next meeting in Montreal on May 28.

He also said that the EWG plans to initiate discussions on how to revise existing variation and supplement regulations and guidelines worldwide to implement ICH Q12. The goal is to initiate these discussions soon after ICH Q12 reaches Step 1/2A in June 2017.

Nasr said that a Step 2B document is expected to be released for public comment in the third quarter of 2017, and a Step 4 guidance is expected in the second quarter of 2018.

From the editors of Gold Sheet. Published online April 3, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Safety issues associated with over-the-counter analgesic combination products used for upset stomach (i.e., heartburn, nausea, fullness, belching, gas, acid indigestion, and/or sour stomach) and hangover indications under the Internal Analgesic and Antacid monographs; discussion of the hangover indication under the Overindulgence, Internal Analgesic and Stimulant monographs	Nonprescription Drugs; Drug Safety and Risk Management	April 4
Novo Nordisk's nonacog beta pegol (recombinant human coagulation Factor IX, glycopegylated) for hemophilia B	Blood Products	April 4
Inspirion Delivery Sciences' oxycodone immediate-release for management of moderate-to-severe pain where the use of an opioid analgesic is appropriate; committees will discuss the overall risk-benefit profile and whether applicant has demonstrated abuse-deterrent properties that would support labeling	Anesthetic and Analgesic Drug Products; Drug Safety and Risk Management	April 5
Development of antibacterial drugs that treat a single species of bacteria when the target species infrequently causes infections	Antimicrobial Drugs	April 13

Pink Sheet

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