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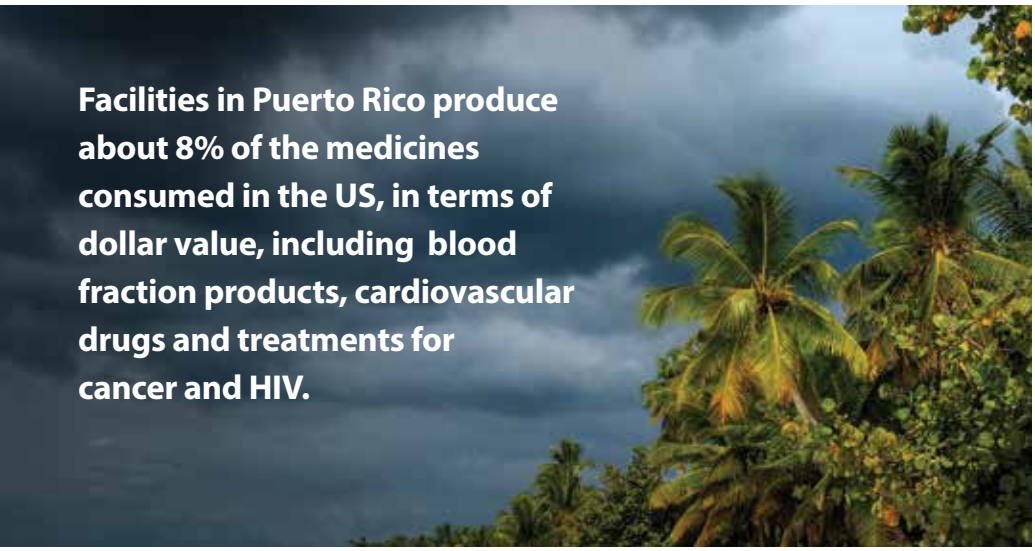
GOTTLIEB: Hurricane Maria May Cause Critical Drug Shortages By Q1 2018

BOWMAN COX bowman.cox@informa.com



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US shortages of certain critical drug products may begin early next year if electrical crews haven't restored power to pharmaceutical manufacturing facilities in Puerto Rico by then, FDA Commissioner Scott Gottlieb told legislators Oct. 24.

Hurricane Maria brought down the power grid when it hit the island Sept. 20. *(Also see "FDA Focusing On Drug Shortage Risks From Puerto Rico Hurricane" - Pink Sheet, 1 Oct, 2017.)*

"My biggest long-term concern right now from a public health standpoint is that we may face product shortages of critical medical products heading into the first quarter," Gottlieb told a House Energy and Commerce oversight and investigations subcommittee hearing. "We're going to do everything we can to head them off."

Another concern Gottlieb raised: if repairs take too long, the pharmaceutical sector might begin to leave Puerto Rico. "If we don't do our job and help these facilities stand back up in a timely fashion, we could start to see some of the production move out of the island, and I think that would put a strain on the Puerto Rico economy."

He noted that the pharmaceutical sector employs 90,000 people in highly paid manufacturing jobs that account for more than 30% of Puerto Rico's gross domestic product. *(Also see "Gottlieb: Why FDA Must Help Restore Puerto Rico's Pharma Sector" - Pink Sheet, 9 Oct, 2017.)*

Facilities in Puerto Rico produce about 8% of the medicines consumed in the US, in terms of dollar value, Gottlieb added in his written statement. Key pharmaceuticals made there include blood fraction products, cardiovascular drugs and treatments for cancer and HIV.

The hearing explored the Health and Human Service Department's preparation for and response to the 2017 hurricane season, focusing on public health impacts of Hurricane Harvey in Texas, Hurricane Irma in Florida and Hurricane Maria in Puerto Rico.

FDA'S EVOLVING RESPONSE

Gottlieb focused his remarks on FDA's evolving response to the situation that has been unfolding in Puerto Rico in the month since Maria hit the US territory.

He said much of the agency's efforts have focused on 30 medically important drugs that he did not identify, and particularly on 14 that are manufactured only in Puerto Rico.

He said the agency has worked with the Federal Emergency Management Agency, the Department of Homeland Security and the Health and Human Services Department, of which it is a part, "to troubleshoot challenges related to getting fuel for

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Novartis exec discusses details around its agreements with CMS for outcomes based payments and indication-based pricing for Kymriah.

ICH Expansion To Bring New Challenges For Global Consensus On Pediatric Extrapolation

https://pink.pharmaintelligence.informa.com/PS121820

The pharmaceutical industry is cautiously optimistic about the ambitious three-year timeline decided by the International Council for Harmonisation for its new guideline on pediatric extrapolation. However, ensuring consensus on this fast-developing concept will be a challenge as more regulators will have a seat at the discussion table as ICH expands.

Declaring Opioid Emergency, Trump Touts FDA Actions, NIH-Industry Partnerships

https://pink.pharmaintelligence.informa.com/PS121854

Proclaiming the opioid epidemic a public health emergency, President points to FDA's prescriber training requirements and withdrawal of Opana ER; Sen. Leahy decries lack of additional funding.

CDC Panel (Barely) Prefers Shingrix Shingles Vaccine Over Zostavax

https://pink.pharmaintelligence.informa.com/PS121841

In 8-7 vote, Advisory Committee on Immunization Practices recommends GSK's Shingrix as preferred shingles vaccine given its higher efficacy compared to Merck's Zostavax.

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generators and raw ingredients for manufacturing processes, as well as the logistics to move finished products off the island."

One early focus was to secure landing rights for planes to carry out products that might otherwise have been destroyed when warehouses flooded.

Later, FDA got more involved in helping facilities obtain diesel fuel for their generators. Last week, it helped obtain medical grade gases for facilities that use them in manufacturing products critical to the blood supply.

Even as logistics challenges to the steady supply of diesel are overcome, there is a growing recognition of the limitations of the generators powered by that diesel.

"Many generators weren't meant to function for months on end," Gottlieb observed.

"Moreover, a lot of facilities can't return to full production on generator power alone. Most are producing at anywhere from 20% to 70% of their normal capacity, based on our informal survey. They won't be able to resume full production until they get back on the power grid. And if they don't return to the grid by the end of this year, we're concerned that we could face multiple potential shortages unless we can also help these facilities temporarily shift more of their manufacturing off the island."

Some pharmaceutical manufacturing facilities in Puerto Rico are "very hardened," and could perhaps operate indefinitely on generators. "But that's the exception," Gottlieb said. "Most of those facilities will not be able to operate for a sustained period of time. … The generators themselves are going to start to break down."

He said the agency is working with partners at HHS and the US Army Corps of Engineers on ensuring the continued viability of a handful of critical facilities.

In certain cases, FDA is working with firms to secure secondary generators. Without these backups, if generators fail and facilities shut down, restart can be difficult and slow, given the loss of continuous directional airflow through the facility and refrigeration of stored batches, he noted. FDA would probably have to re-inspect them prior to restart.

> "Most plants running on generator power "are producing at anywhere from 20% to 70% of their normal capacity [but] will not be able to operate for a sustained period of time. … The generators themselves are going to start to break down."
> – Gottlieb

SURGERY LIGHTED BY CELL PHONE

Another issue is the re-emerging power grid's instability. Authorities have made it a priority to get Puerto Rico's hospitals back on the electrical grid, and 60% of them are, according to Robert Kadlec, assistant secretary of health for preparedness and response, who also testified at the hearing.

However, several committee members raised concerns about lack of stability, with Rep. Jan Schakowsky, D-Illinois, recalling a photograph of surgeons after they lost power, working on a patient by the light of a cell phone flashlight.

Kadlec said HHS is working with FEMA to make sure that hospitals have backup generators and access to a FEMA repair team to fix the primary generator if it goes down.

AN HOMAGE TO THE WORKERS OF PUERTO RICO

Gottlieb paid homage to the local workforce, saying, "if we do avert critical shortages, it will be primarily because of our fellow citizens who returned to their posts at this critical time, even as their own families were displaced and their lives devastated. We owe them all an enormous debt of gratitude."

He also called attention to the efforts of pharmaceutical manufacturers to help the island recover. They're using their facilities as disaster relief stations, distributing FEMA aid to outlying towns. They're distributing gasoline, water, food and batteries to employees and using their cafeterias to feed workers and their families. One even shipped thousands of generators to the island for distribution to their employees.

"Most of all, I want to recognize the resilience of the people of Puerto Rico and their fidelity to our public health mission," Gottlieb said. "FDA has a long history of operating on the island. It's been an integral part of our work. We owe the island's residents our steadfast and long-term commitment to a full recovery."

From the editors of the Gold Sheet.
Published online October 24, 2017

Brexit Hits Life Science Investment Decisions As UK Risks Exclusion From Key EU Projects

IAN SCHOFIELD ian.schofield@informa.com

The continuing uncertainty over the UK's future relationship with the EU has started to influence some long-term investment decisions by service companies that support the life science sector, and there is a danger that the UK will lose its ability to attractive global talent and expertise unless the status of EU nationals in the country is clarified urgently.

Moreover, the UK runs the risk of being excluded from several key EU initiatives that it played a major part in creating, notably the Falsified Medicines Directive with its pan-European product verification system, the EudraVigilance database of adverse drug reactions, and the new Clinical Trial Regulation which offers a single trial submission portal and central database.

These and other issues posed by Brexit were raised during the latest hearing of the House of Lords' Science and Technology Committee on Oct. 24, as part of the committee's wide-ranging inquiry into Life Sciences and the Industrial Strategy.

Those giving evidence to the committee included Mike Thompson, chief executive of the Association of the British Pharmaceutical Industry, Steve Bates, CEO of the BioIndustry Association, and Nisha Tailor, head of policy and public affairs at the Association of Medical Research Charities.

On the Brexit front, Bates observed that the UK's departure would have different effects on different parts of its life science ecosystem. "If you've got fantastic science, and you need money to essentially fund some experiments to take it further down the translation pipeline, that is fairly straightforward and is unaffected by Brexit."

But, he continued, "if you're involved in anything that is regulated by a single European system which we have grown up with for the last 40 years, there is significant risk and uncertainty… fundamentally the rules of game are up in the air and we don't know where they are going to go."

He said that the uncertainty was already having an impact in terms of investment plans in the sector. "There is significant risk and businesses are making decisions on this as we speak – this is quite fundamental, there is quite a large chunk of service businesses that support the research infrastructure, people who operate in a clinical research environment. It is significant for people who are making investment decisions now for the long term, we are a long cycle business."

"I think it has had an impact on investment decisions in the last three months, and we would echo the position of the CBI and others about concerns around that," Bates said, referring to a letter sent to Brexit Secretary David Davis by five UK business groups, including the Confederation of the British Industry and the British Chambers of Commerce, calling for a transition period of at least two years after Brexit and warning about the consequences of the UK leaving the EU without a deal.

Amid Brexit uncertainty, difficult decisions will have to be made.

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> "Fundamentally the rules of game are up in the air and we don't know where they are going to go"
> – BIA CEO Steve Bates

Reiterating the industry's insistence on some sort of post-Brexit regulatory cooperation framework to avoid divergences between the UK and the EU, Thompson said there was "a health security issue here, you have to put patients first." For example, he said, at the moment the EU has a single pharmacovigilance database. "It doesn't make sense for the UK to have own database, it makes sense to continue to have one pharmacovigilance database. Patients will benefit from us picking up anything that comes in through Heathrow and then goes onto the continent of Europe. So we are all in this together."

INDUSTRY JOINT DOCUMENT

Thompson also told the committee that the BIA and the ABPI had produced a joint document, "signed off by our European associations, that says this is what we collectively want, and the reason is that if we don't have cooperation, the impact will be the same across Europe."

Asked whether this was a public document, Thompson said, "No, it's an industry document, so we will be careful about showing that." However, he added that the substantive points in the document were "well known, we have talked about them publicly."

In addition, he noted that several biopharmaceutical industry bodies had written to Davis and the EU's chief negotiator, Michel Barnier, in July, outlining the importance of securing ongo-

ing cooperation between the UK and the EU as part of the Brexit negotiations.

Among other things the letter stated that in the event of an "unorderly withdrawal," there was a "risk that all goods due to be moved between the UK and EU could be held either at border checks, in warehouses or manufacturing and/or subject to extensive retesting requirements," which would lead to "severe disruption of most companies' supply chains" and "potential supply disruptions of life-saving medicines." It too called for an "implementation period" to give companies time to "transition to a new framework."

THE UK AND KEY EU INITIATIVES

One question yet to be answered is whether the UK will be able to benefit from the provisions of the new Clinical Trial Regulation, which will apply in the EU member states from the fourth quarter of 2019. Among other things the CTR will bring a single application portal for clinical trials across the EU together with a central trial database run by the European Medicines Agency.

It was suggested recently that because the CTR's provisions will apply after the Brexit date of March 29, 2019, they will not be covered by the Repeal Bill that will transpose all EU legislation into UK law. *(Also see "Delay Means New EU Clinical Trial Rules May Not Be Transferred To UK" - Pink Sheet, 17 Oct, 2017.)*

Bates said the CTR was "a complex piece of work that was developed over a period of years and will be implemented over a period of years, and in the middle of that implementation period we have potentially a Brexit or a transition period."

"We now face the prospect of the rules of the game being fundamentally changed in a direction we believe will be better," Bates said of the CTR. "But will we be allowed to play in that game or not, that is the challenge we are facing. There are some quite difficult things here around the date of Brexit, whether we will be able to have access to the centralized database when the EMA puts that together, how we might integrate with that medicines agency or not."

Thompson brought up another landmark initiative that the UK played a key part in developing: the Falsified Medicines Directive, under which an EU-wide product verification framework is being constructed, with a "unique identifier" for each individual product pack and a "repositories" system for detecting fake products.

> "Fundamentally the rules of game are up in the air and we don't know where they are going to go"
> – BIA CEO Steve Bates

This, said Thompson, will "provide enormous benefits, and it will also ultimately give useful data to the supply chain. So that also is about to come – the industry has invested tens of millions of pounds to ensure it can be implemented and it would be unfortunate if only UK patients were not protected against counterfeit medicines. So these are things we have all fought for together and we want patients to be able to benefit."

RESEARCH PROGRAMS

The committee also asked whether the UK would be able to continue its participation in the EU's Horizon 2020 research funding program and whether UK researchers would be able to move freely between the UK and the continent.

Tailor said a number of charities that belonged to her organization took part in Horizon 2020, and "the message is that funding is important, but just as important are the collaboration opportunities that arise from Horizon 2020. We would certainly welcome continued access to those programs, including the IMI [Innovative Medicines Initiative] that is part of that."

She added that it was also crucial to ensure the UK remains attractive to global talent and expertise, "so we need urgent clarification on the status of EU nationals, particularly those working in health and research." The UK, she said, would also need "an immigration system that recognizes the collaboration and international nature of science and takes into account the breadth of people involved in life sciences, from researchers to entrepreneurs, innovators and technicians."

Views expressed on the UK's Life Science Strategy by witnesses to the committee's inquiry will be covered in a future article in the Pink Sheet.

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

EMA's Clinical Data Policy One Year On: 50 Products, 3,000 Documents And 'Positive Feedback'

IAN SCHOFIELD ian.schofield@informa.com

Clinical study reports on 50 medicines, including orphans, biosimilars, generics and pediatric drugs, have been made publicly available since the European Medicines Agency's policy on the proactive publication of clinical data was launched a year ago, the EMA has announced.

"This amounts to 3,279 clinical documents, totalling more than 1.3 million pages," the agency said. "The majority of the data relates to the approval of new medicines, but there is also data for medicines that are already authorised and for which an extension of their clinical use has been sought," it observed.

Under the proactive publication policy, researchers and academics can directly access, download and re-evaluate clinical reports on a drug's safety and efficacy that have been submitted with centralized approval applications.

The data are published on the EMA's clinical data publication (CDP) website once the decision-making process for a drug has been completed, regardless of whether it has been approved for marketing by the European Commission, withdrawn by the sponsor, or rejected.

The website has two access modes – general information purposes, and "academic and other non-commercial purposes" (allowing download, saving and re-analysis of the data).

The most recent data made available on the website relate to the following two products:

- **GlaxoSmithKline PLC**'s *Umbipro*, a gel formulation of chlorhexidine digluconate for the prophylaxis of omphalitis (infection of the umbilical cord) in newborns, which in April 2016 was given a positive opinion for use in countries outside the EU. Under Article 58 of Regulation (EC) No 726/2004, the EMA's key scientific committee, the CHMP, can give its opinion on a product intended mainly for use in developing countries, which is then used by national regulators to make their own approval decisions.
- **Janssen Inc.**'s *Imbruvica* (ibrutinib) for patients with previously untreated chronic lymphocytic leukemia, an expanded indication that gained EU approval in May 2016.

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87% of users said data were "presented in an understandable format, despite the redaction or anonymisation of certain information" – EMA

Other new products/indications to feature recently include **Mylan Laboratories Ltd.**'s *Mysildecard* (sildefanil) for pulmonary arterial hypertension, **Shire Pharmaceuticals Ireland Ltd.**'s *Revestive* (teduglutide) for short bowel syndrome in children, and **AbbVie Inc.**'s *Humira* (adalimumab) for pediatric Crohn's disease.

SURVEY FINDS POSITIVE REACTIONS

A total of 3,641 users have accessed data under the policy so far, resulting in 22,164 document views and 80,537 downloads for "non-commercial research purposes," according to the EMA.

The agency said it had conducted a survey of web users in which 60% of respondents said the data provided were useful, and 87% that they were "presented in an understandable format, despite the redaction or anonymisation of certain information in line with European legislation on personal data protection." Participants in the survey included researchers, healthcare professionals, patients and industry.

Three quarters of respondents to the survey agreed that the proactive publication of clinical data "helps EMA to build public trust and confidence in its scientific and decision-making processes," while two thirds agreed that it helped researchers to re-assess the clinical data, the agency said. Full results of the survey are to be published in due course, it added.

According to the EMA, publication of clinical data under the policy helps in "the independent re-analysis of data after a medicine has been approved and enhances scientific knowledge." The greater transparency "facilitates knowledge sharing, leading to more efficient medicine development programmes and ultimately benefitting innovation," it said.

The implementation of the policy was initially fraught with controversy, with some companies claiming it risked disclosing confidential information and could be used by generics firms to seek approvals of their own versions of originator drugs. The policy does allow sponsors to redact information that is considered to be genuinely commercially confidential, although at the end of December last year companies expressed concern about the time and effort required to do so. *(Also see "'Give Us More On Warning On Publishing Our Clinical Data,' Industry Implores EMA" - Pink Sheet, 25 Jan, 2017.)*

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

China Sets Norms For Foreign Trial Data Submissions

BRIAN YANG brian.yang@informa.com

China FDA released on Oct. 20 a new draft pertaining to clinical trial data that specifies requirements for foreign drug makers to use study data obtained outside China towards a new product approval in China.

Per the draft, data from a global parallel study or multi-regional clinical trial (MRCT) can be used towards a product registration in China, if it meets certain clinical data requirements.

Marketing authorization holders "should ensure the data's authenticity, integrity, accuracy and traceability, and subject to inspection from China Food and Drug Administration," noted the CFDA draft, titled Technical Requirement for Acceptance Of Overseas Clinical Trial Data, issued by the agency's new drug review subsidiary, Center for Drug Evaluation (CDE).

The regulatory scrutiny includes data integrity inspections, noted the CDE. "A whole set of clinical trial data should be filed towards obtaining a NDA in China, and there should be no selective filing," the draft says. "Ensuring clinical trial and data integrity is the basic requirement for the acceptance of a NDA filing."

For parallel studies where China is a part, sponsors should combine domestic and foreign data into a complete data package. And for a new drug that has not been marketed worldwide, a complete data package should be filed, and if the product is marketed, the product's post-marketing safety and efficacy information should be filed, in addition to the clinical data.

Foreign sponsors who have completed early-stage studies and contemplate conducting late-stage studies in China should consult the CDE and supply the center a complete foreign clinical data package, the draft advises. It is open for public comments until Nov.25 [Click here for the draft: Chinese language].

"It benefits multinational drug makers in China, and encourages MRCTs and parallel studies," noted a long-term clinical study professional working for a MNC drug maker in China.

Another notable aspect emphasized by the agency is requirements around ethnic difference studies. The CDE requires marketing authorization holders to analyze efficacy and safety among Chinese patient population against overall population groups. It also encourages regional and race sensitivity analysis to support the efficacy and safety assessment.

"Following ICH efficacy assessment guidelines E5 (Ethnic Factors in the Acceptability of Foreign Clinical Data), [MAH holders should] analyze the China patient subgroup against overall population groups to support extrapolation of foreign clinical data to Chinese patient population," noted the draft.

Additional technical requirements include compliance with ICH's Good Clinical Practice (GCP).

CONDITIONAL APPROVAL

The agency outlined three outcomes on submission of foreign clinical data:

1. Complete Accept: When data integrity meets GCP and clinical data audit requirements; efficacy and safety supports the indication; ethnic sensitivity analysis show no impact on the efficacy and safety profile.
2. Partial Accept: When data integrity meets GCP and data audit requirements; efficacy and safety supports the indication. But ethnic sensitivity analysis shows an impact on the efficacy and safety profile; data extrapolation uncertain.
3. No Accept: Which implies major data integrity issues; foreign data is insufficient to support indication, or ethnic sensitivity analysis shows impact on efficacy and safety profiles.

As to treatments for critical, rare and pediatric diseases, foreign data can be partially accepted and conditional approval can be granted subject to post-market efficacy and safety assessment, said the agency.

Major infectious diseases including multi-drug resistant tuberculosis (MDR-TB), HIV/AIDS and certain cancer types including lung, liver cancer are considered critical diseases in China.

One such treatment is **Johnson & Johnson**'s *Sirturo* (bedaquiline) for MDR-TB. The first new treatment to fight in decades to fight tuberculosis gained CFDA approval in Dec. 2016, based on Phase II study data, noted the clinical trial professional.

DATA AUDITS

Legal experts suggest that foreign study sponsors eyeing the new pathway should prepare for data audits from the CFDA.

In a bid to crack down on data forgery and other GCP violations, the CFDA has waged a massive campaign – the key measure is data audits. Study sponsors are required to ensure data integrity and NDA filings are subject to clinical site inspections from the agency.

"Both the complete and partial accept of foreign data could face potential clinical data inspections," said Chen Yang, partner at international law firm Sidley Austin.

From the editors of PharmAsia News. Published online October 24, 2017

Finally, Drug Pricing Consensus: There's No 'Silver Bullet' For This Werewolf

MICHAEL CIPRIANO michael.cipriano@informa.com

A regular gun with lead bullets won't put down a werewolf; at least that's what legend says. One must pierce the heart of the fearsome, mythological creature with a silver bullet to the heart, as its purification properties can purge the monster of its demonic DNA.

Unfortunately, no silver bullet exists to defeat the unique werewolf of high drug prices. At least that's what a growing chorus of voices in the Rx policy sphere is saying.

Rep. Frank Pallone, D-N.J., is among the frustrated monster hunters, noting that "one thing alone" will be a solution to more affordable drug prices.

Speaking at the Center for American Progress a few moons ago, Pallone – who serves as ranking member of the House Energy and Commerce Committee – laid out a menu of legislative items he would like to see Congress take up.

He first touted the creation of a robust generic marketplace as "a major way to try to deal with drug prices effectively," while noting that the House "addressed generics to some extent in the user fee bill."

The House-passed version of the user fee bill includes several provisions related to generics, including eight-month priority reviews for abbreviated new drug applications (ANDAs) when no more than three approved generics exist or the reference product is on the US FDA's drug shortage list and the establishment of a breakthrough-style review program for generics. *(Also see "User Fee Bill Or Drug Pricing Bill? House Members Makes Both Cases" - Pink Sheet, 12 Jul, 2017.)*

Pallone also discussed a series of proposals that did not make it into the user fee reauthorization bill, such as legislation that would stop innovators from using Risk Evaluation and Mitigation Strategies to prevent generic sponsors from obtaining samples of the brand product, allow the Centers for Medicare and Medicaid Services (CMS) to negotiate Medicare Part D drug prices directly with pharmaceutical companies and authorize "CMS and participating state Medicaid programs to partner with private sector contractors to negotiate supplemental rebates from drug manufacturers."

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> "There is no silver bullet. "There are a lot of marginal things you can do in the aggregate that will lower costs. And we are looking for those marginal things."
> – Sen. Cassidy

The congressman also cautioned Democrats not to treat Medicare drug price negotiations as the silver bullet to solving drug pricing.

HARDLY THE FIRST TO USE THE PHRASE

Pallone has not been the first in the drug pricing policy circle to vocalize the increasingly used phrase for solutions to kill the one-of-a-kind werewolf.

In a statement on a Democrat-proposed bill called the "Improving Access to Affordable Prescription Drugs Act," Sen. Elizabeth Warren, D-Mass., said that, "There's no silver bullet to lower drug prices, but this bill offers a menu of solutions to tackle the drug pricing problem and help bring down health costs for everyone."

The term has also been used by Republicans. Sen. Bill Cassidy, R-La., used the phrase at the Alliance for Patient Access' biosimilar summit in April.

"There is no silver bullet," Cassidy said. "There are a lot of marginal things you can do in the aggregate that will lower costs. And we are looking for those marginal things."

A Senate Republican staffer used the term in January in noting that no single solution exists to solve the pricing problem and preserve innovation. *(Also see "Trump, Congress And The Search For Common Ground On Drug Pricing" - Pink Sheet, 18 Jan, 2017.)*

The phrase has additionally picked up steam among industry itself. Biotechnology Innovation Organization CEO wrote in a New York Times letter to the editor in May that, "There is no silver bullet for rising health costs." Steve Miller, Chief Medical Officer at Express Scripts, said in a December 2016 statement that no silver bullet exists "to solving the problem of high drug prices."

Drug firms, and the health care industry in general, can't be happy about having their products analogized to demonic beasts. Companies can only hope that the phase of the moon changes and the public moves on to other worries – or that Congress is populated by Taylor Lautner fans.

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The Great Rebate Debate: Why Do They Exist?

MICHAEL MCCAUGHAN michael.mccaughan@previsionpolicy.com

The first question from Senate Health Education Labor & Pensions Committee Chairman Lamar Alexander (R-Tenn.) during the committee's Oct. 17 drug pricing hearing demonstrates the triumph of the pharmaceutical industry's campaign to broaden the discussion around prices.

The discussion that followed is a sign that there are limits to that success.

After hearing opening statements by witnesses from across the supply chain, Alexander began by noting the testimony about the total amount of rebates (which he pegged at $100 billion per year) and the challenge of understanding where that money goes.

"We've been working on health insurance, which we find to be very complicated," Alexander said. "Where the money goes in prescription drugs is even more complicated. I've yet to figure out where the money goes." He then asked a seemingly simple question. "Why do we need rebates at all?"

Alexander's question – and, indeed, the focus of the hearing itself – underscores the success of the brand name industry's efforts to shift attention away from manufacturer pricing actions and onto the complex economics of the drug supply chain.

Coming into 2017, the Pharmaceutical Research & Manufacturers of America launched a campaign to highlight the difference between list prices and the net price realized by brand companies, focusing attention on rebates, distribution channels and insurance designs that impact the amount paid by consumers at a pharmacy counter.

The goal was to deflect efforts to enact "transparency" legislation away from a strict focus on manufacturer margins and onto the broader pharmaceutical marketplace. *(Also see "Drug Pricing 'Opacity,' Degrees Of Transparency Debated By National Academies Panel" - Pink Sheet, 10 Jan, 2017.)*

The fact that the second drug pricing hearing of 2017 would focus specifically on that issue is a sign of how successful the PhRMA campaign has been. The Oct. 17 hearing including witnesses from various trade associations in the supply chain, including PhRMA, the generic industry (Association for Accessible Medicines), wholesalers (Healthcare Distribution Alliance), retail pharmacy (American Pharmacists Association) and the pharmacy benefit management sector (Pharmaceutical Care Management Association).

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> Manufacturers and PBMs offered very different explanations for why rebates exist.

Somewhat predictably, the testimony itself included a significant amount of finger-pointing among the various witnesses. PhRMA also came into the meeting armed with a new study focused on a key element of the system not represented at the hearing: hospitals, where (the PhRMA-funded study says) prescription drugs are typical marked up 250%.

NO ONE DEFENDS REBATES

Alexander's opening question cut through a lot of that finger-pointing – and may in fact be a sign that the debate over the flow of rebate dollars has all but played out. Alexander appeared to catch the witnesses somewhat flat-footed by asking why rebates are even necessary – but it demonstrated that none of the organizations present was ready to defend rebates as necessary or even useful.

Alexander posed it initially to American Pharmacists Association CEO Thomas Menighan, who fumbled for words and didn't directly answer. Later in the hearing, however, Menighan returned to the question and made clear that "we oppose rebates in all their forms."

Association for Accessible Medicines CEO Chip Davis noted that generic companies typically don't pay rebates, and instead already follow the model of negotiating direct, up-front price reductions.

Healthcare Distribution Alliance SVP Elizabeth Gallenagh attempted to abstain, saying "wholesalers don't have a role" in the price/rebate dynamic. Pressed by Alexander, she said eliminating rebates is "something to be explored."

"That's what we are doing. We are exploring it," Alexander shot back.

That leaves the two principals in the debate over rebates: manufacturers and PBMs. Neither industry group defended rebates – but they offered very different explanations for why they exist.

Alexander asked Pharmaceutical Care Management Association CEO Mark Merritt first about "getting rid" of rebates. "We'd be open to that," Merritt answered. "Rebates were around before PBMs ever came on the scene" and are also used in other sectors, he observed. Typically, Merritt said, rebates are used because manufacturers want "to keep a high price" for some purchasers while making concessions to bigger buyers.

PhRMA EVP Lori Reilly argued instead that rebates are driven by the demands of payors and PBMs. "High rebates are things that PBMs and insurer companies like," she said. They generate a separate revenue stream and "they get a big check at the end of the day that they can use as they like."

"Would you, Ms. Reilly, like to eliminate rebates?" Alexander asked. "We'd like to see rebates get passed back to the patient at the point of sale," she said.

But Alexander wasn't satisfied. "Why worry about a big chart that shows how they are being passed back? Why not just

eliminate rebates?"

"That is one option obviously, to just have a lower list price," Reilly said. "But I will tell you today, plans and PBMs tend to favor products, in terms of formularies, … with a high price and high rebate because that money tends to flow back to them to decide what to do with."

PBMS HAVE THE BETTER TALKING POINT

The exchange underscores the challenge PhRMA has set for itself: the trade association is simultaneously attacking rebates as a hidden source of costs to consumers while defending them as a necessary evil for commercial success. Merritt, on the other hand, came into the hearing with a much more straightforward message: PBMs want the lowest net cost and don't care what mechanism gets that.

In a subsequent exchange over insulin prices with Sen. Bill Cassidy (R-La.), the benefits of PCMA's posture were apparent. Reilly quibbled with Cassidy over figures showing the relative rates of growth in list prices and rebates in the insulin class – but Cassidy politely but firmly stuck to his argument that the higher list prices were in fact driving higher costs to patients. "Somebody's paying. Its either indirectly through a premium or directly through a copay, but somebody's paying."

Turning to Merritt, he noted Mylan's claims that the dramatic price increase for *EpiPen* was driven by the need to provider higher rebates to maintain formulary positions in the face of competition.

"I would disagree" with Mylan, Merritt said. "Mylan raised the price 400% just because they felt like doing it."

Cassidy repeated Mylan's assertions that higher list prices are a competitive necessity, because without rebates the company couldn't stay on formulary. "I don't think that happened. The reality is if they lowered the price that would make it great too. All we want is the lowest net cost," Merritt replied. "The simplest thing is if lower their prices."

No one should expect a serious push to eliminate rebates in the near term given the lack of momentum for any significant pricing legislation at this point. And even if there were to be a push for legislation, it is hard to fathom a straightforward approach to prohibiting rebates.

The Medicaid program, for example, includes a statutory rebate on prescription drugs, while Medicare Part D is premised on the idea that PBMs are negotiating rebates and discounts in a market where manufacturers set premium prices for exclusive products. Even if federal statutes and program rules were changed to eliminate rebates, it is not clear how the practice could be eliminated in the setting of private market sales.

That leaves the issue as a very safe topic for "exploration" in the context of hearings – but perhaps one that is not likely to consume that attention for much longer.

From the editors of the RPM Report. Published online October 26, 2017

Biosimilar Firms Fight Against 'Whisper Campaign' On Interchangeability

DERRICK GINGERY derrick.gingery@informa.com

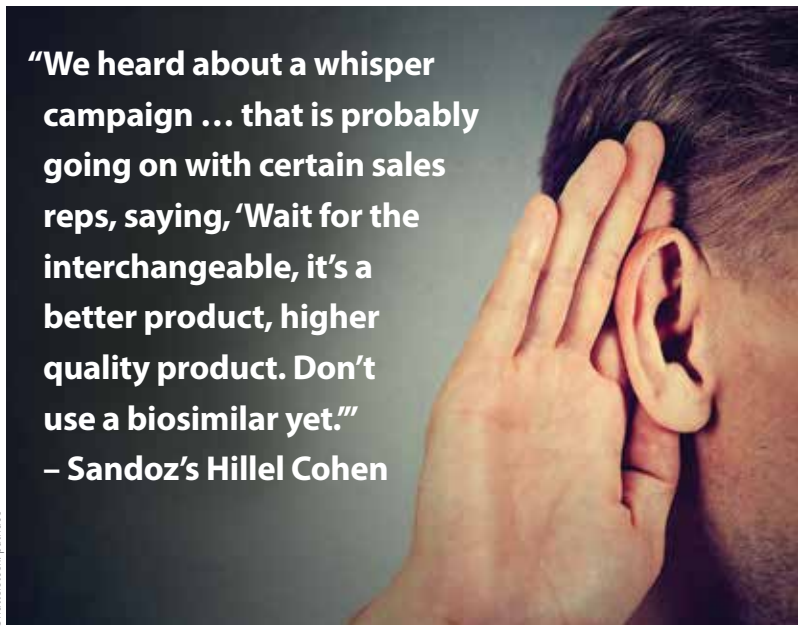
Biosimilar sponsors are worried that interchangeability, or lack thereof, could be used against them by reference product manufacturers to limit uptake and question product quality.

Because interchangeability is considered a higher bar for FDA approval than biosimilarity, sales representatives, presumably for innovator products, have suggested to providers that they should wait for the biosimilar to receive interchangeability status before using it, said Hillel Cohen, **Sandoz Inc.** biopharmaceuticals unit executive director of scientific affairs.

"We heard about a whisper campaign … that is probably going on with certain sales reps, saying, 'Wait for the interchangeable, it's a better product, higher quality product. Don't use a biosimilar yet,'" Cohen said during the Association for Accessible Medicines' recent Leading on Biosimilars conference.

The argument plays on the perception that interchangeable products are considered superior to biosimilars because they require additional review and approval.

While biosimilar sponsors dispute the premise, the campaign could have a substantial impact on biosimilar uptake if it is widely



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embraced, as well as potentially devalue a biosimilar approval.

Cohen said a biosimilar and interchangeable product are not different from each other. "The molecule itself is the same," he said. "If you're going to refine it to make it better in some manner or form, it's no longer the biosimilar. It has to go through the entire regulatory process itself. So, it is the same product. Same molecule, same formulation."

Interchangeability status means that studies have shown that a patient can switch between the reference and biosimilar without any change in the clinical effect. Earlier this year, FDA released long anticipated guidance on how the sponsors could gain the designation. *(Also see "Biosimilars: Postmarketing Data Alone Not Enough For Interchangeability" - Pink Sheet, 17 Jan, 2017.)*

FDA has yet to approve any interchangeable products, and it doesn't appear the agency has even received any for review. With uncertainty about the standards to gain the designation, sponsors have been slow to embrace it.

Some sponsors had argued that interchangeability was important to the development of the biosimilar market in the US. But with the national debate over drug prices still ongoing and payers looking for cost-cutting opportunities, many believed that simply gaining approval as a biosimilar would be enough to support market uptake. *(Also see "Biosimilar Interchangeability May Be Losing Luster As Approval Goal" - Pink Sheet, 13 Sep, 2016.)*

However, the market particulars have proven demanding for biosimilars, so much so that **Pfizer Inc.** has sued **Johnson & Johnson** claiming the firm coerced payers by vowing to withhold all *Remicade* rebates if any of Pfizer's infliximab biosimilar *Inflectra* is reimbursed. In response, J&J says Pfizer has failed to show the value of Inflectra *(Also see "Pfizer v. J&J Sets Stage For Biosimilar Showdown Over Exclusive Contracts" - Pink Sheet, 20 Sep, 2017.)*

FDA has yet to approve any interchangeable products, and it doesn't appear the agency has even received any for review. With uncertainty about the standards to gain the designation, sponsors have been slow to embrace it.

Boehringer Ingelheim GMBH in July became the first company to publicly disclose that it had started a clinical trial intended to support an interchangeability application. It's VOLTAIRE-X study is intended to show that its proposed biosimilar *Cyltezo* (adalimumab-adbm) is interchangeable with **AbbVie Inc.**'s *Humira* (adalimumab). *(Also see "Humira Biosimilar Interchangeability: The Race Begins" - Pink Sheet, 30 Jul, 2017.)*

The announcement was a vote of confidence in the product, coming before Cyltezo was approved in August. *(Also see "Humira Biosimilar: Boehringer Faces Same Launch Hurdles As Amgen" - Pink Sheet, 28 Aug, 2017.)*

Sandoz also has publicly stated its interest in pursuing interchangeability determinations for its biosimilars, but has yet to disclose an application. The clinical studies in its biosimilar applications were thought to be intended to support an eventual interchangeability application. *(Also see "Sandoz's Multi-Switch Biosimilar Trials: A View To Interchangeability?" - Pink Sheet, 21 Jul, 2016.)*

EDUCATION NECESSARY TO FIGHT MISINFORMATION

It may be difficult to separate the perception that interchangeability coincides with superiority, given that there are more requirements for interchangeable products.

FDA's website states that interchangeable products meet "additional standards," that show it can be "substituted for the reference product by a pharmacist without the intervention of the health care provider" who prescribed it.

The agency added that biosimilars and interchangeable products meet its rigorous standards for safety and efficacy, meaning patients and providers can rely on them as they would the reference product.

FDA also has been preparing a communication campaign for providers about biosimilars and interchangeable products that is expected to be unveiled this fall. The agency told the Pink Sheet that it is developing materials intended to increase:

- Understanding of biologics, reference products, biosimilars and interchangeable products
- Awareness of FDA's role in the biosimilar approval process
- Knowledge of the data and information FDA reviews to determine biosimilarity

Cohen said that biosimilar sponsors and advocates have to educate stakeholders about the meaning of interchangeability. He also said manufacturers, physicians and patient groups must understand the difference between the designations.

"There's been a lot of advertising for a lot of these biologics," Cohen said. "Patients will come to their doctors and their pharmacists with pre-conceived notions. So, I think patient advocacy groups, they will as well."

Claire Saxton, senior director of education for Cancer Support Community, an education and patient support organization, said her group's material would generally follow FDA statements.

"When we're providing our education, what we're going to say is here's what the FDA says about biosimilars and here's what the FDA says about interchangeable products," she said. "Nothing in what we produced would say one is superior to the other."

FDA said its campaign will "provide helpful information to healthcare providers about the approval standards for biosimilar and interchangeable products," including how both are reviewed to ensure they meet the agency's high approval standards.

The agency already has indicated that it would target its biosimilar education messages at providers immediately impacted by the approved products. *(Also see "FDA Biosimilar Education Campaign Will Need To Be Targeted" - Pink Sheet, 17 Sep, 2015.)*

As part of the biosimilar user fee program renewal, FDA also

committed to enhancing its staff to improve public understanding of biosimilarity and interchangeability. *(Also see "Biosimilar User Fee Agreement Offers FDA Funding Boost, Fee Structure Overhaul" - Pink Sheet, 16 Sep, 2016.)*

WALKING THE SUPERIORITY LINE

Several in the innovator biologics industry were careful not to say specifically that interchangeable products are superior, but did highlight that its requirements are tougher than those for biosimilarity.

In comments on FDA's draft interchangeability guidance, the Pharmaceutical Research and Manufacturers of America said that interchangeability was a high standard that required additional data beyond what is necessary for biosimilarity.

AbbVie, which has been defending its biologics from biosimilar competition, called the interchangeability review "much more demanding than the biosimilarity assessment," in guidance comments.

The Biotechnology Innovation Organization said interchangeability was a "more extensive standard than biosimilarity" and legally and scientifically distinct from it.

"Demonstrating interchangeability requires an additional, more extensive showing," BIO wrote in guidance comments.

Biosimilar and biologics sponsors also disagreed in comments on whether US-licensed reference products should be used in switching studies to show interchangeability. *(Also see "US Comparator Requirement For Interchangeable Biosimilars Would Hurt Industry" - Pink Sheet, 31 May, 2017.)*

LATEST IN GROWING LIST OF BIOSIMILAR ISSUES

The interchangeability perception issue seems to be the latest problem to emerge as the biosimilar market grows.

Non-medical switching, a term that has been used to describe changing a patient that is stable on a biologic to the biosimilar for non-clinical reasons, even though it is not deemed interchangeable, has emerged as a concern from some patient groups.

Advocates have called on FDA to make a public statement against the practice *(Also see "Biosimilar Non-Medical Switching: Advocacy Groups, FDA Advisors Push For Action" - Pink Sheet, 14 Jul, 2016.)*, and opponents have invoked the concept in arguments that biosimilars and their reference products are different. *(Also see "Lobbying FDA: AbbVie Questions Humira Biosimilars In Private Meeting" - Pink Sheet, 5 Aug, 2016.)*

Several states also have passed laws requiring a pharmacist to notify a physician after substituting a prescribed brand product for an interchangeable biosimilar. *(Also see "Biosimilar Substitution: 'Devil' Is In Barriers To Switch In State Laws" - Pink Sheet, 25 Jan, 2016.)*

The biosimilar industry also is lobbying CMS to change its policy of using one reimbursement code for reimbursement of all biosimilars referencing the same product.

Beyond any shifts in the policy landscape, the basic mechanics of getting biosimilars to market remain challenging, particularly the patent dance, a dynamic illustrated most recently by an agreement between AbbVie and **Amgen Inc.** to delay launch of a Humira biosimilar until 2023.

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PTC To Appeal Translarna's Complete Response Letter From US FDA

SUE SUTTER sue.sutter@informa.com

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PTC Therapeutics Inc.'s plans to appeal a US FDA complete response letter for *Translarna* (ataluren) could once again make Center for Drug Evaluation and Research (CDER) Director Janet Woodcock the decision-maker on a Duchenne muscular dystrophy drug that the agency's own clinical reviewers have concluded lacks substantial evidence of efficacy.

On Oct. 25, a day after the user fee goal date for ataluren, PTC announced that FDA's Office of Drug Evaluation I (ODE I) had issued a complete response for treatment of nonsense mutation dystrophinopathies, including Duchenne muscular dystrophy (DMD).

FDA's complete response letter "indicated that evidence of effectiveness from an additional adequate and well-controlled clinical trial(s) will be necessary at a minimum to provide substantial evidence of effectiveness," PTC said. "The letter also mentioned other nonclinical and [chemistry, manufacturing and controls] matters that PTC is in the process of addressing."

In a press release, CEO Stuart Peltz said the company is extremely disappointed for the Duchenne community and strongly disagrees with the agency's conclusions.

"We believe that this decision fails to consider the benefit/risk of ataluren and the high unmet medical need," Peltz said. "Therefore, we plan to file a formal dispute resolution request next week."

APPEALING TO A HIGHER AUTHORITY ...

The rejection of the new drug application is hardly a surprise given that FDA filed the NDA under protest after twice refusing to file it due to lack of substantial evidence of efficacy. *(Also see "'File Over Protest' At US FDA: PTC To Pursue Rarely-Used Pathway For DMD Drug" - Pink Sheet, 9 Jan, 2017.)*

In September, 10 of 11 members of FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted that while it is possible ataluren may be effective in treating dystrophinopathies resulting from nonsense mutations in the dystrophin gene, the data are inconclusive and more work would be needed to establish efficacy. *(Also see "Patients Can't Clear Translarna's Data Hurdles As PTC Falls Short At FDA Panel" - Pink Sheet, 28 Sep, 2017.)*

Panelists pointed to the failure of two randomized, placebo-controlled trials to meet their prespecified primary endpoints. Although post hoc, exploratory analyses suggested benefit, they were not persuasive evidence of efficacy, committee members said, generally agreeing with agency reviewers' opinions of the data. *(Also see "Exondys Revisited? Translarna Brings Efficacy Woes Into US Panel Review" - Pink Sheet, 26 Sep, 2017.)*)

With an appeal of the complete response letter, PTC will seek to move beyond the negative reviews by the advisory committee, the Division of Neurology Products and ODE I to a higher authority.

Pursuant to FDA's September 2015 draft guidance on formal dispute resolution appeals above the division level, an appeal of the ODE I complete response letter would first go to the Office of New Drugs (OND).

> "FDA's letter states that "evidence of effectiveness from an additional adequate and well-controlled clinical trial(s) will be necessary at a minimum to provide substantial evidence of effectiveness," PTC said.

Woodcock has been serving as acting director of OND since longtime office head John Jenkins retired in January. Presumably, any appeal to OND would wind up on her desk or that of OND Deputy Director Peter Stein.

Even if Stein were to deny the appeal, PTC could continue up the chain of command to the CDER director's office and, ultimately, to Commissioner Scott Gottlieb.

... AND PUTTING THEIR FAITH IN WOODCOCK?

PTC appears to be hoping that Woodcock will do for ataluren what she did for **Sarepta Therapeutics Inc.**'s exon-skipping DMD treatment *Exondys 51* (eteplirsen).

In September 2016, Woodcock granted eteplirsen accelerated approval after overruling the objections of clinical review staff who believed substantial evidence of efficacy had not been demonstrated. Woodcock concluded that the quantity of dystrophin production produced in the eteplirsen clinical trials was reasonably likely to predict clinical benefit. *(Also see "Sarepta's Eteplirsen Approved After Contentious Internal FDA Debate" - Pink Sheet, 19 Sep, 2016.)*

The CDER director described her decision as representing the greatest flexibility possible while remaining within FDA's statutory framework. However, ODE I Director Ellis Unger said the approval would lower the evidentiary standard for effectiveness, and he appealed to then-Commissioner Robert Califf.

Califf ultimately deferred to Woodcock on the approval decision, concluding that the approval was "unique situation" that would not lower the bar for other drugs under the accelerated approval pathway. *(Also see "Accelerated Approval After Eteplirsen: A Lowered Bar Or A Unique Event?" - Pink Sheet, 20 Sep, 2016.)*

Nevertheless, at the ataluren advisory committee meeting PTC pointed to the eteplirsen approval as precedent for FDA's exercise of regulatory flexibility in considering the totality of the data for rare disease treatments.

In the eteplirsen proceedings, Woodcock drew internal criticism for her frequent interactions with the patient community and Sarepta, as well as her participation in the advisory committee review. In contrast, Woodcock did not attend the ataluren advisory committee meeting, although Stein did.

Also unlike with eteplirsen, accelerated approval does not appear to be a pathway for ataluren because FDA officials have described the dystrophin production data as uninterpretable due methodological shortcomings. *(Also see "How Accelerated Approval Works – And How It Doesn't" - Pink Sheet, 28 Sep, 2017.)*

TOTALITY OF THE EVIDENCE

In its appeal, PTC can be expected to argue that regulatory flexibility is warranted given the rare disease setting, high unmet need and totality of efficacy and safety evidence.

Even though ataluren failed the prespecified endpoints in two clinical trials, subgroup and post hoc analyses showed evidence of benefit. At the advisory committee meeting, numerous patients and family members testified that the drug had slowed disease progression and maintained walking ability far longer than predicted based upon the natural history of the disease.

PTC also can be expected to highlight real-world experience in countries where the drug is approved and comparisons of ataluren patient outcomes against natural history data.

Ataluren is the second drug intended to treat DMD to receive an FDA complete response letter in the past few years. **BioMarin Pharmaceutical Inc.** terminated the development of *Kyndrisa* (drisapersen), an exon-skipping treatment, in 2016 following an FDA complete response letter. *(Also see "BioMarin Kills Kyndrisa, But Duchenne Pursuit Not Over" - Pink Sheet, 1 Jun, 2016.)*

BioMarin had considered appealing the drisapersen CRL following eteplirsen's approval, but apparently opted against it. "We continue to develop second-generation molecules, which we believe are substantially better compounds with potentially

superior efficacy, and would therefore be more likely to succeed through all phases of development and registration," a company spokesperson said.

In early 2017, the agency approved **Marathon Pharmaceuticals LLC**'s corticosteroid *Emflaza* (deflazacort), making it the second drug approved for DMD after eteplirsen. *(Also see "Keeping Track: US FDA Approves Emflaza And Parsabiv, Turns Down Opioid/Anti-Emetic Combo CL-108" - Pink Sheet, 12 Feb, 2017.)* PTC acquired the drug from Marathon in March after the launch was complicated by a pricing controversy.

MESSAGE TO THE DMD COMMUNITY

In a statement to the Pink Sheet, FDA said it could not comment on questions about ataluren because information about an application that has yet to receive an approval, or has received a complete response, generally is not releasable by the agency.

However, FDA "recognizes the unmet medical need of patients with Duchenne muscular dystrophy, a devastating disease for patients and their families. We remain committed to addressing the urgent need for new treatment options."

"We have taken a number of steps in recent months to advance and support the development of orphan drugs, and will continue to look for opportunities to specifically support the advancement of DMD treatments," FDA said. "In just over a year, the agency has approved two new treatments for DMD patients, but we understand that much more is needed and recognize the importance of bringing new treatment options to this community. We will continue to work closely with the community and all companies to expedite the development and approval of safe and effective drugs to treat this disease."

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FDA's NDA And BLA Approvals: Bydureon Bcise, Shingrix

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				
AstraZeneca	*Bydureon Bcise* (exenatide extended-release)	2 mg once-weekly formulation of the GLP-1 receptor agonist, administered with an auto-injector, to be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	S, 3	10/20/2017
Xellia	Daptomycin	350 mg/vial for injection for the treatment of adults with complicated skin and skin structure infections (cSSSI) and Staphylococcus aureus bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.	S, 5	10/20/2017
Liss America	Carbon dioxide	Medical Gas		10/20/2017
New Biologics				
GlaxoSmithKline	*Shingrix* (zoster vaccine recombinant, adjuvanted)	Prevention of herpes zoster (shingles) in adults aged 50 years and older.		10/20/2017

KEY TO ABBREVIATIONS	
Review Classifications	**NDA Submission Classification**
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

England's NICE Takes Tough Stance On Opdivo; No Relief from Cancer Drugs Fund

JOHN DAVIS john.davis@informa.com

Three anticancer products that have been rejected by England's National Institute for Care and health Excellence in draft guidance are unlikely to be listed in the Cancer Drugs Funds (CDF) because there are no ongoing clinical trials to provide additional data. This means companies will have to come to an agreement with the health technology assessment body on pricing before the product can be made available on the English National Health Service.

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BMS will negotiate on pricing for Opdivo in bladder cancer

"Companies need to come to the table with their best, most realistic price offer right at the start." - NICE

The drugs are **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab), **Eisai Co. Ltd.**'s *Lenvima* (lenvatinib) and **Pfizer Inc.**'s *Nexavar* (sorafenib).

In the case of Opdivo, NICE is not recommending the PD-1 inhibitor for use as an option for advanced urothelial cancer in patients already treated with platinum-containing chemotherapy even though it accepts the drug "is likely to extend people's lives by more than three months".

Extending lives by more than three months is usually accepted by the English HTA body as a meaningful clinical benefit. However, the incremental cost-effectiveness ratio (ICER) would be between £67,205 and $86,030 per QALY gained (compared with paclitaxel and docetaxel respectively). "This is higher than NICE normally considers acceptable for end-of-life treatment," says the NICE draft guidance.

The NICE committee responsible for the appraisal also could not recommend placing Opdivo in the CDF for bladder cancer because there are "no planned or ongoing studies that could address the key clinical uncertainties identified."

BMS has faced similar issues with NICE before. Earlier in October, the agency recommended nivolumab for use within the CDF in certain patients with head and neck cancer, after initially saying that evidence relating to its effectiveness in the condition was uncertain. BMS agreed to collect further data on how patients respond who access it from the CDF, and from a clinical trial, and this satisfied NICE.

Also, in September, Opdivo was made available through the CDF for use in patients with lung cancer after a similar deal was struck with NICE. The company agreed to make the product available at a discount while clinical trials were ongoing.

NICE had strong words to say about the negotiating techniques of pharmaceutical companies after concluding the lung cancer agreement on Opdivo. "Companies need to come to the table with their best, most realistic price offer right at the start, so we get new exciting drugs, such as immunotherapies, to patients as quickly as possible," it said.

Other checkpoint inhibitors are being assessed for bladder cancer by NICE, including **Roche**'s *Tecentriq* (atezolizumab) and **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab).

LENVIMA, NEXAVAR

Eisai's Lenvima and Pfizer's Nexavar have been rejected as options for treating advanced differentiated thyroid cancer that has spread to other part of the body and cannot be operated on, according to draft NICE guidances issued on Oct. 20. The ICERs were much higher than normally considered to be cost effective, so they could not be recommended for routine NHS use, NICE said. The Institute also noted there were no significant ongoing clinical trials that could provide more evidence on survival benefit, that would allow NICE to consider the drugs for the CDF.

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Indian Panel Nudges Eisai Towards Phase IV Compliance For Halaven

ANJU GHANGURDE anju.ghangurde@informa.com

A subject expert committee (SEC), which advises the Indian drug regulator on trial-related approvals and marketing clearances, has declined to permit a Phase IV trial waiver for **Eisai Co. Ltd.**'s *Halaven* (eribulin mesylate) in India.

The SEC (oncology and hematology), at its meeting earlier this month, noted that Eisai had failed to conduct the Phase IV study for the product "even after more than two years from the date of approval".

Halaven was granted a conditional approval in 2013. "The condition of approval was to complete the study within two years after launching the product in the market, though 3,712 patients have been treated with the drug in India as presented by the firm," the SEC observed at its Oct. 13 meeting.

Eisai Pharmaceuticals India Pvt. Ltd. is said to have presented the SEC with data on 79 patients from "published literature", which includes two abstracts (53 patients) and two case series (26 patients).

The SEC, however, opined that this data is "not scientifically sufficient to waive off the Phase IV trial in India".

Previously, the SEC (then known as New Drugs Advisory Committee) had recommended Halaven for marketing authorization without local Phase III trials subject to the condition that a Phase IV clinical trial on 200 patients be conducted in India. The committee, at the time, stipulated that the study should be completed within two years of launching the product on the market.

There have, over the recent past, been a few instances of seeming post-facto requests from companies for tweaks in post-marketing studies in India, with some experts suggesting that the Indian regulatory apparatus should perhaps have "strict guidance" on all protocol review and similar requests. **Boehringer Ingelheim GMBH** had earlier this year sought tweaks in the surveillance plan for nintedanib in India amid disinclination among some physicians to participate in the study. *(Also see "Did Novo Nordisk Sidestep Protocol Requirements For Novoeight In India?" - Pink Sheet, 19 Apr, 2017.)*

PUBLISHED LITERATURE CONFIRMED SAFETY/EFFICACY

Eisai does not appear to be intent on appealing against the SEC's latest decision rejecting its request for a Phase IV trial waiver. "We acknowledge the decision of the SEC and will follow the necessary requirements," the company told the *Pink Sheet*. Eisai added that it has "always abided" by the law of land and the "directions" given by the regulatory authorities both state and central.

The company said it acknowledged the "significance" of Phase IV trials, since these trials are "intensive and specified," and they often test the drug's effect on specific demographics over a period of time.

"In this case Halaven's safety and efficacy in the Indian population was to be evaluated in the Phase IV trial. Since Halaven was in the market for over three years and used extensively in over 3,700 metastatic breast patients across India, Eisai decided to request for a Phase IV waiver," the company explained.

An expert panel said Eisai had failed to conduct the Phase IV study for the product "even after more than two years from the date of approval."

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Eisai also confirmed that the data presented to the SEC pertained to 79 Indian patients. "The published literature confirmed that the safety and efficacy of Halaven was in-line/similar to that presented in the international Phase III pivotal studies," it added.

Eisai had, at the time of initial application for Halaven in India also specified, among other details presented, that eribulin showed no ethnic differences in the pharmacokinetic data between Japanese and US populations. Besides, it had noted that chemotherapy practices for breast cancer management is 'near similar' between India and other countries, and in the absence of pharmacokinetic differences due to sex, race or age with eribulin, it believes that safety and efficacy data obtained in the US/EU and Japan could be extrapolated to Indian patients.

Halaven was approved in India in April 2013 for the treatment of locally advanced or metastatic breast cancer previously treated with at least two chemotherapy regimens including an anthracycline and a taxane. Eisai had, at the time, also introduced a tiered-pricing model for Halaven in which the cost burden to patients is differentiated according to income level, ranging from full payment by the patient to total reimbursement by the Japanese company. *(Also see "Eisai Fortifies Play With India-Specific Priced Fycompa" - Pink Sheet, 23 Aug, 2017.)*

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Decision Against Attorney Fees In Mucinex Patent Claim Could Resonate

EILEEN FRANCIS eileen.francis@informa.com

A federal court decision that frees **Reckitt Benckiser Group PLC**from paying attorneys' fees to a firm awarded a rare summary judgement to dismiss RB's complaint on patents for its *Mucinex* OTC expectorant could encourage drug firms' inclination to file patent infringement litigation.

Judge Leonard Stark of the US District Court for the District of Delaware says RB's patent infringement complaint against Indian firm **Aurobindo Pharma Ltd.** and its East Windsor, N.J.-based **Aurobindo Pharma USA Inc.** division for infringement of two *Mucinex DM* patents was reasonably filed, maintained and litigated and is not sufficiently distinguished from other patent litigation to deem it "exceptional," which is necessary for a defendant to be awarded attorneys' fees.

Under federal laws for patent infringement litigation, a court can award reasonable attorneys' fees to a prevailing party provided the case is considered "exceptional" in some manner, including that it is "frivolous" or that it is "simply one that stands out from others with respect to the substantive strength of a party's litigating position or the unreasonable manner in which the case was litigated," according to Stark's Oct. 16 order.

In a complaint filed in 2014 by its Reckitt Benckiser LLC subsidiary, RB argued that Aurobindo's proposed abbreviated new drug application for a cough and cold equivalent to Mucinex DM (dextromethorphan/guaifenesin; extended-release tablet) infringed the product's patents on controlled-release formulations of guaifenesin containing both immediate- and sustained-release portions and quantities.

The UK manufacturer and marketer of health, hygiene and home products contended Aurobindo's product appears to contain two distinct formulations because the ANDA's dissolution profile demonstrates it releases guaifenesin in a manner similar to Mucinex DM's two-rate dissolution profile. However, RD did not analyze Aurobindo's ingredient list or provide evidence regarding the physical structure of the generic product to demonstrate it includes more than a single formulation,

Approving Aurobindo's motion for summary judgement of non-infringement, Stark in March said no reasonable fact-finder could find that, as asserted by RB, Aurobindo's proposed ANDA product contained two distinct formulas. Instead, the ANDA shows only that the Indian firm sought FDA approval of a single formulation, extended-release product.

While the judge approved Aurobindo's summary judgement motion, he noted that he did not accept all of the firm's arguments.

"On balance and considering the totality of the circumstances, the court concludes that the factors weighing against finding this case exceptional outweigh those in favor. While the evidence garnered by Reckitt to support its infringement claims was insufficient to overcome Aurobindo's motion for summary judgement, the court does not find that this case – whether compared to the full panoply of patent cases with which the court has been involved or with the more narrow category of ANDA cases it has handled – stands out with respect to the substantive strength of Reckitt's unsuccessful positions or the manner in which Reckitt litigated the case."

RB also is the target of antitrust litigation Mutual Pharmaceutical Co. Inc. filed in 2015 claiming the UK firm breached a 2007 settlement in which Mutual agreed to refrain from entering the OTC extended-release guaifenesin market until another manufacturer began offering generics of Mucinex.

Aurobindo received FDA approval for guaifenesin/dextromethorphan 600 mg/30 mg and 1,200 mg/ 60mg extended-release tablets in March, according to the firm. During its second-quarter earnings briefing in August, Aurobindo Managing Director Govindarajan said the firm launched the products for US private label and store brand customers in the spring and was "ramping up" volumes at retailers.

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With automatic 30-month stays of FDA approvals of ANDAs triggered when patent litigation is filed, "the court should be alert to the incentives branded drug companies like Reckitt have to file frivolous cases." – Aurobindo Pharma

AUROBINDO ARGUES BIG PICTURE

Aurobindo followed up by arguing in court that RB's filing was "exceptional" in terms of standing out from similar patent cases, Stark noted in his ruling the motion for attorneys' fees.

The Rx generic and OTC private label drug firm urged Stark to consider the larger

impact on the industry from his summary judgement dismissal of RB's complaint. Aurobindo argued for attorneys' fees based on RB's "claim construction and infringement theories in light of the need to deter abusive ANDA litigation" in the future.

Aurobindo referenced the Hatch-Waxman Act's purpose to foster "timely entry of generic drugs to market" as an important consideration in the decision. The firm stated with an automatic 30-month stay of FDA approval of an ANDA triggered when patent litigation is filed, "the court should be alert to the incentives branded drug companies like Reckitt have to file frivolous cases."

The court also "should perhaps be more willing to find an ANDA case exceptional" within the meaning of federal law, Aurobindo argued.

Aurobindo referenced the Hatch-Waxman Act's purpose to foster "timely entry of generic drugs to market" as an important consideration in the decision.

JUDGE FINDS MERIT IN RB ARGUMENT

Stark weighed the merits of Aurobindo's argument to deem the case "exceptional." He noted the litigation stands out because it was resolved on summary judgement, "a rare occurrence in this court, which often does not allow summary judgements motions to be filed in an ANDA case."

However, that rarity wasn't enough to justify ordering RB to pay Aurobindo's legal fees.

Stark said "this fact alone does not make this case per se 'exceptional.' That the nature of the narrow dispute presented by the parties turned out to be amenable to summary judgement does not inevitably correlate to an exceptionally weak substantive position or an unreasonable manner of litigation."

Still, he was critical of RB given that its complaint against Aurobindo is similar to its 2011 patent infringement litigation against **Watson Laboratories Inc.** also for a Mucinex patent. An appellate court upheld a district court ruling that RB's two formulas-in-one patent infringement claim against Watson did not hold up. *(Also see "Perrigo Sets Generic Mucinex Launch After Patent Claim Decision" - Pink Sheet, 16 Jan, 2012.)*

Despite its failure with that approach with Watson, though, RB again asserted an infringement theory "without regard to the structure of the formulation," Stark stated. "Reckitt's litigation strategy, thus, was unusual."

On the other hand, the judge found multiple factors weighing against deeming the case exceptional. "Reckitt performed a reasonable investigation on the ANDA product after filing the case, including by performing testing," including devoting resources to generate evidence regarding other claims as limitations as well, Stark said.

Further, the company's argument supporting its complaint were not "wholly unreasonable or without merit" and is not "entirely devoid" of an infringement theory, the judge added. "Reckitt performed testing on the ANDA product, retained an expert to provide opinions about the testing, and presented a coherent – although ultimately unsuccessful – theory of infringement."

From the editors of the Tan Sheet.
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US FDA Commits To Meeting With Complex ANDA Sponsors, Works Hard To Avoid It

DERRICK GINGERY derrick.gingery@informa.com

In creating opportunities for early interaction on complex generic product development, the US FDA may have excited sponsors, but at the same time the agency also gave itself an incentive to prevent the system's use.

Absent product-specific guidance on a complex generic or an alternative equivalence evaluation where a development guidance has been issued, agency officials must allow sponsors the pre-ANDA product development meeting.

It already appears that FDA is not interested in conducting too many development meetings, if possible. Robert Lionberger, director of the Office of Research and Standards in FDA's Office of Generic Drugs, said the agency wants to update its guidances in part to avoid scheduling the meetings.

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"We have the incentive to get those product-specific guidances updated because if we don't get ahead of you, then you can come in and meet with us and say we're actively developing this," Lionberger said during an Oct. 20 workshop on developing generic topical dermatologic products.

The new pre-ANDA meeting process is intended to allow generic drug sponsors a chance to receive scientific and other advice from FDA before a complex product application is submitted. It was included among the FDA commitments for the renewed generic drug user fee program, which began Oct. 1 *(Also see "Complex ANDAs To Be Allowed Pre-Submission Product Meetings" - Pink Sheet, 24 Oct, 2016.)*

MEETING METRICS COULD ADD TO WORKLOAD

Meetings can be difficult to schedule and time-consuming. They require preparation by FDA staff, which takes away from review and other activities, as well as follow-up work, and are not the most efficient way of disseminating the agency's view to industry.

In fiscal years 2018 and 2019, the agency is expected to grant or deny 90% of product development and pre-submission meeting requests within 30 days of receipt. The goal increases to within 14 days in FY 2020, FY 2021 and FY 2022, according to the GDUFA II commitment letter. The agency must conduct 60% of the meetings within 120 days of granting them in FY 2018. The goal increases to 70% in FY 2019, 80% in FY 2020 and 90% in FY 2021 and FY 2022. FDA can meet the goal by either conducting a meeting or providing a meaningful written response that will inform drug development within the goal date, according to the commitment letter.

Scheduling metrics have proven difficult for FDA to accommodate already. FDA's biosimilar program struggled to meet some of its product development meeting goals in the early years of that user fee program. *(Also see "FDA Met Biosimilar Review Timelines But Missed Meeting Goals In 2015" - Pink Sheet, 25 Apr, 2016.)*

If the agency can update or issue new generic product-specific development guidances, it can avoid at least some of the complex generic meeting workload. "Either way we're working hard," Lionberger said. "We're advancing on both fronts."

The work associated with ANDA review and approval has been much higher than anticipated, in part because of the multiple review cycles needed to approve applications. *(Also see "There's The Bolus! ANDA Sponsors Race To Avoid User Fee Spike" - Pink Sheet, 9 Oct, 2017.)*

Product development and pre-submission meetings are available to sponsors, where specific scientific questions or the content of the application can be discussed, respectively. FDA also could schedule a mid-review cycle meeting to discuss issues that have emerged during the review. The hope is that the meetings prevent multiple review cycles for the products, which can lead to speedier approvals. *(Also see "Complex ANDAs: Early Meetings With FDA Can Generate Bonus Communication" - Pink Sheet, 2 Oct, 2017.)*

> The new pre-ANDA meeting process is intended to allow generic drug sponsors a chance to receive scientific and other advice from FDA before a complex product application is submitted.

> FDA has issued 51 product-specific guidances, including 32 new and 19 revised documents, with expectations for generic development.

FDA also developed an electronic platform for meeting requests.

PRESSING ISSUES CAN FORCE GUIDANCE UPDATES

While meetings have strict metrics, guidance writing also is a difficult and time-consuming process. Lionberger admitted that there are hundreds of topical products that will require new or updated guidances, meaning it will take a while to produce them. He asked for feedback on areas where the agency should focus.

"If we see there's this topical product and everyone's interested and it's something we don't know about in the marketplace, that's useful and actionable information for us that feeds into what … the topical team there work on next," he said.

Sam Raney, scientific lead in the OGD Division of Therapeutic Performance, said the agency is continually updating product-specific guidances, "as soon as we have a new standard that we think is applicable to a certain class."

But OGD Deputy Director John Peters said if a specific situation warrants, it could make changes outside its regular schedule. "We'll sometimes find through surveillance or through other means that we missed something," he said. "In those situations we'll revise the guidance more rapidly because that would be clear evidence that the guidance that we currently have was inadequate."

The agency announced Oct. 20 that it had issued 51 product-specific guidances, including 32 new and 19 revised documents, with expectations for generic development.

FDA's focus on complex products is part of its efforts to increase generic competition in the hopes of bringing down drug pricing. The agency recently approved the first generic of **Teva Pharmaceutical Industries Ltd.**'s *Copaxone* 40 mg (glatiramer acetate injection) after several years of review. *(Also see "Copaxone 40mg Generic: FDA Exceeds Mylan's Expectations" - Pink Sheet, 5 Oct, 2017.)* But executives at **Mylan NV**were publicly frustrated with the process, saying administrative issues held up the complex ANDA. *(Also see "Mylan Suggests Downside To FDA's Efforts To Improve Generic Drug Review" - Pink Sheet, 9 Aug, 2017.)*

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How To Find And Remedy Data Integrity Lapses In Microbiology Labs

JOANNE EGLOVITCH joanne.eglovitch@informa.com

Data integrity lapses discussed in recent drug GMP warning letters were not confined to the analytical chemistry laboratory but showed up in the microbiology laboratory as well, an FDA official said. The official outlined a three-step approach to resolving such problems that FDA often describes in such warning letters.

To avoid enforcement action, pharmaceutical manufacturers should adopt a more tailored approach to conducting internal data integrity audits of microbiological labs, an industry expert said. This approach should be different than audits used in analytical chemistry labs. The expert also said that manufacturers should not underestimate the impact of an employee's personal and professional problems on data integrity.

These approaches were explored Oct. 17 at the Parenteral Drug Association's annual microbiology meeting in Bethesda, Md.

FDA's Paula Katz, director of manufacturing quality guidance and policy in the Office of Compliance in the agency's Center for Drug Evaluation and Research, said that data integrity is a recurring and growing problem found in drug GMP warning letters. An FDA analysis of the 45 drug GMP warning letters the office sent to domestic and foreign drug manufacturers between Jan. 1 and July 17, 2017, found that half had data integrity problems.

Katz stressed that data integrity lapses can bedevil microbiology labs, and not just analytical chemistry labs. She said that "there is a bit of a misperception that data integrity plays a role only in the analytical lab and we are talking about chromatography and fancy high-tech computerized instrumentation. That is not true at all. I hope to dispel that myth."

WARNING LETTERS SHOW DATA INTEGRITY FAILINGS IN THE MICRO LAB

She said that some of the common data integrity issues in the microbiological lab that surface in warning letters include missing, manipulated or fabricated data; failing to report plate counts; failing to collect environmental monitoring samples; and missing microbiological sample plates and tubes from incubators when FDA inspectors arrive for inspections.

Katz went over five examples from recent warning letters in showing how data integrity failings are very much alive and well in the microbiology lab:

- Failure to record incubation dates of the microbiological plates, and to record and maintain the raw data to support colony counts on microbiological plates;
- Deleting audit trails for instruments used to test sterile products;
- Discarding original lab and production records, and placing these records in trash bags behind the plant;
- Missing in-progress microbiological test plates for finished drug products; and
- Back-dating and falsifying laboratory data.

THREE-STEP REMEDIATION PROGRAM

FDA expects manufacturers to remediate such problems through a three-step program, said Katz. The three-step program is often described in warning letters. The program should include a comprehensive investigation of the problem, a risk assessment to ascertain the extent of the problem, and a management strategy that should include corrective actions taken to address the problem.

The comprehensive assessment should detail the extent of the inaccuracies in data reporting. It should summarize all labs and manufacturing operations subject to the lapses.

Katz noted that there is a correct way – as well as an incorrect way – to conduct these assessments. She described two manufacturer's responses to a 483 observation.

First an incorrect example: a firm had 30 products yet only assessed seven products with no explanation for its choice.

A correct example: a firm used a random sampling of all batches and provided statistical justification for the sampling size.

As part of this assessment, current and former employees should be interviewed to identify the nature, scope and root cause of data inaccuracies. The agency recommended that qualified third parties conduct these interviews so employees feel comfortable in discussing questionable actions of their employers.

Manufacturers should also conduct a risk assessment on the potential effects of the observed failures on the quality of the marketed drugs. The risk assessment should analyze the risk to patients caused by the release of drugs affected by data integrity lapses.

Manufacturers should also have a management strategy in place, which is the global corrective and preventive action plan. The management strategy should describe the interim measures to protect patients and ensure drug quality. These measures can include notifying customers, recalling product or adding lots to stability programs, and enhancing complaint handling.

BY THE TIME FDA ARRIVES IT IS TOO LATE

Katz said that by the time that FDA comes to inspect the firm and finds data integrity problems, this can be symbolic of larger problems within the company.

She also said that "if we are able to come in and find something in a very short period of time that means there is a lot more going on."

Katz noted that FDA's expectations on ensuring data integrity were spelled out on in draft guidance issued last year. *(Also see "FDA Collates GMP Data Integrity Advice Into New Guidance" - Pink Sheet, 28 Apr, 2016.)*

DIFFERENT APPROACHES NEEDED

Dennis Guilfoyle, senior director of microbiology and analytical regulatory compliance for **Johnson & Johnson**, discussed how firms can audit their microbiology operations for data integrity compliance before FDA inspectors come knocking at the door. Guilfoyle worked at FDA for 40 years as a microbiologist before going to J&J.

He said that in some ways data integrity problems in the microbiology lab may be more difficult to address than similar failings in analytical chemistry labs.

Guilfoyle said, "in the chemistry world, there is a computer within an analytical process where you can follow paper trails, but in the microbiology lab, the work is mostly performed manually and is frequently based on individual observations from an individual scientist." This information is entered either on paper or submitted into a laboratory information management system (LIMS).

Therefore, he said, it is important for auditors to interview the analysts who conducted the microbiological tests. This is the only way to figure out if employees are being told by supervisors to suppress undesirable lab results.

He said that "there may be occasions where a supervisor or senior analyst may tell a junior analyst how to handle a unique appearance of an unwanted microorganism found growing on petri plates. The informal instruction may be something like, 'before recording the type or total number of colonies viewed on the petri plate they should hand deliver that petri plate to a supervisor.'"

Or another red flag is raised when an analyst is told to write the numerical count of the suspected colonies on the lid of the petri dish but to not record this on the official worksheet until the supervisor or senior analyst has a chance to review it.

Auditors should also be aware of some "red flags' when reviewing analytical work sheets:

- The lab is reporting more tests than can be reasonably run per day or week;
- The worksheets are completed by lab personnel not present on the day of the test;
- The worksheets are approved by someone other than the lab supervisor;
- The worksheets have changes in the handwriting or signature of the employee;
- The worksheets have changes in the reporting of colony forming units from numerical units to zero;
- The worksheets are perfectly filled out worksheets, suggesting they are a second copy;
- The worksheets are either missing or out of order; and
- The worksheets have results from a single batch reported twice.

RELIABILITY CAN BE AFFECTED BY PERSONAL PROBLEMS

Guilfoyle said that firms should also be aware that personal or professional problems can affect an employee's job performance, and potentially undermine the quality of the data emanating from the lab.

He said that "I want to bring this to light because these problems are the basis for the root cause of a lot of data integrity problems."

He said that the performance of the microbiologist can be affected by:

- Lack of physical well-being, such as fatigue from working two jobs;
- Personal problems such as family or marital issues or disputes between co-workers;
- Alcohol or substance abuse;
- Inadequate on the job training;
- Pressure to meet quotas or timeframes; and
- Personal ambition or doing what it takes to satisfy the boss.

He said that it is incumbent on laboratory managers to be able to recognize how these factors can impede job performance.

"The first line supervisor needs to be able to verify and check the reliability of the data coming out of the laboratory. There is nobody more important than the first line supervisor when overseeing the reliability of the work and the integrity of the individuals. I see it as a very simple solution. I think a lot of these problems would go away if first line supervisors did their jobs."

Yet he acknowledged that overseeing a large lab staff as well as a heavy workload can complicate these efforts.

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No Amendments Any Time Soon For EU Paediatric Regulation, Says Hotly Awaited Report

NEENA BRIZMOHUN neena.brizmohun@informa.com

The European Commission will not be proposing any amendments to the controversial EU Paediatric Regulation any time soon – at least not before 2019, when the results of a new study evaluating the combined effects of the legislation and the Orphan Regulation are expected to become available.

This was just one of the conclusions drawn by the commission in its newly published – and much-awaited – report on how the regulation is working 10 years after it came into force.

Whether the report would lead to revisions to the Paediatric Regulation (Regulation (EC) No 1901/2006) had been a key issue for drug companies, which in the past have complained that the legislation is overly prescriptive and onerous. *(Also see "'Not What We Expected,' R&D Industry Says Of 'Onerous' EU Paediatric Regulation" - Pink Sheet, 12 Jul, 2017.)*

The report, published on Oct. 26, found that the regulation has had a "considerable impact" on the development of pediatric medicines in the EU, but that there are still therapeutic areas where the benefits of the legislation have yet to become evident.

It also found that while the combination of obligations and rewards under the regulation seemed "effective to shift focus to paediatric product development," only 55% of the completed pediatric investigation plans (PIPs) had benefited from a reward. In addition, it said that the EU's pediatric-use marketing authorization (PUMA) tool, with its specific reward, had "failed to deliver."

Weaknesses identified in the report often relate to pediatric diseases that qualify as an orphan condition, the commission notes. Therefore, the commission says that before it proposes any revisions to the Paediatric Regulation, it will need to take a closer look at the combined effects of the regulation and the Orphan Regulation through a joined evaluation of the two legal instruments. "Only such a combined effort will guarantee" that the right parameters are adjusted, if required, it said. The aim is to deliver the results from the evaluation by 2019.

In the meantime, the report sets out a series of "concrete actions" the commission plans to take to streamline the application and implementation of the regulation. These include analyzing experience with the use of PIP deferrals and considering changes in practice to ensure the speedier completion of PIPs.

BEFORE AND AFTER

A comparison of the situation regarding the development of pediatric medicines before and after the Paediatric Regulation took effect demonstrates a clear positive effect in terms of new authorized medicines for children, according to the report.

In 2007-2016, more than 260 new medicines for use in children (new marketing authorizations and new indications) were authorized, most of them linked to the regulation's requirements. The number of agreed PIPs surpassed 1,000 in 2017, of which 131 were completed at the end of 2016. "There is a clear upward trend in the number of completed PIPs, with over 60% finalised in the last three years," the report notes.

EU report on how the Paediatric Regulation is working after 10 years is now published

All these figures are also in line with expectations, "taking into account that bringing a medicinal product to the market may take up to 10 years, underlining the incremental change the Regulation provides."

At the same time, issuing a marketing authorization or adding pediatric information to existing marketing authorizations does not automatically translate into the immediate availability of the product to all paediatric patients in the EU, the commission says. This may be due to pending reimbursement decisions at national level or to prescribing habits where physicians may not directly switch to newly authorized products.

The report also says that while the increase in pediatric research and the number of new products with specific pediatric indications is encouraging, these positive results are not evenly spread among all therapeutic areas. The regulation works best in areas where the needs of adult and pediatric patients overlap, it found.

Problem areas concern diseases that are rare and/or unique to children and which, in many cases, are equally supported through the orphan legislation. Here, major therapeutic advances have rarely materialized. "Why this is the case and why the orphan reward is in some instances not able to drive paediatric development in a similar way than adult orphan development requires further scrutiny," the report says.

PROBLEMS WITH THE REWARDS

The report notes that the regulation places an additional burden on pharmaceutical companies by asking them to carry out pediatric research that they might not have undertaken otherwise.

On the other hand, the regulation links this obligation with a reward system to allow companies to recuperate the additional

> "Figures suggest that up to now only 55% of the completed PIPs benefited from a reward" – European Commission report

upfront costs incurred: a six-month extension to the supplementary protection certificate (SPC), and the orphan reward – a two-year extension of the orphan market exclusivity period, i.e., up to 12 years. The rewards are mutually exclusive and serve different purposes, but both have the effect of delaying the market entry of competitor products.

While the assumption is that products falling within the PIP requirement should be eligible for the reward once the pediatric development is completed, "in reality not all companies were able to obtain a reward," the report says.

"Figures suggest that up to now only 55% of the completed PIPs benefited from a reward. Most of them took the form of a prolongation of the SPC. In a few cases the market exclusivity period of an orphan medicinal product was granted."

The commission expects that the proportion of products that benefit from the reward will increase over time as companies start to plan their pediatric research "better and earlier." But it says "it is unlikely that the success rate will ever reach 100%."

SPCS CONSIDERED MORE PRECIOUS

The SPC prolongation is often considered as the most precious reward, the commission notes. Up to the end of 2016, more than 40 medicines had benefited from the SPC reward. "The number of SPC prolongations granted in the last 10 years (more than 500) shows that companies regularly receive the reward from the national patent office to which they apply," the report says. "This points to a functioning reward system."

On the other hand, because SPCs are national titles – meaning that extensions must be obtained from the national patent office in each EU member state where an SPC exists – they are considered by some to involve an overly complex procedure.

"Moreover, filing for the SPC extension must happen two years before the expiry of the certificate. In some cases, this resulted in companies missing out of the reward as they failed to complete the PIP on time."

THE COSTS TO INDUSTRY

The report refers to an external economic study which looked at costs associated with the regulation. The study found that the total cost for the whole industry was around €2.1 billion per year. Total R&D costs on average amounted to €18.9 million per PIP, with each plan including an average of three clinical studies. "On top of this, companies incur overhead costs of around €720,000 in relation to filing of the initial submission of a PIP and for subsequent modifications."

The report also compares the costs with the value of the SPC reward. Eight medicinal products were analyzed, including medicines that received SPC extensions and lost their protection before the end of 2014. "The data shows that the price drop of branded products often starts in the first quarter after the loss of exclusivity, but limited in scale (up to 20%), before decreasing further," it says.

"There are significant differences between products and countries, most likely linked to the competitiveness of the particular therapeutic market and/or national policies to stimulate generic substitution, leading to a high variation of the economic value of the SPC extension as a percentage of the total revenue (between 10 and 93%). Overall, the adjusted economic value of the SPC reward for the eight products concerned amounts to €926 million, with revenues especially geared towards some blockbuster products included in the sample size."

Based on a model developed as part of the economic study, two of the eight products showed a strongly favorable benefit-cost ratio for health systems when calculated over a 10-year period – i.e., the benefits for society and health in monetary terms outweigh the additional costs due to the extra monopoly rent. All other products had a negative benefit-cost ratio over 10 years, especially those for which the completion of the PIP did not result in a new pediatric indication.

According to further analysis from the economic study, a more conservative estimated rate of return from an annual €2.1 billion investment in pediatric R&D could, after 10 years, yield a total societal return of around €6 billion. "This estimated societal return is significantly higher than the economic value of the SPC extension, suggesting that in monetary terms, the benefits of the Regulation for society outweigh the costs of the additional monopoly rent."

The report notes that the commission is currently evaluating the usefulness of the SPC Regulation. Findings from this evaluation are expected in the coming months and are to be taken into account when the commission looks into whether the Paediatric Regulation needs to be revised.

ORPHAN REWARD

As for the other type of reward available under the regulation, the report says that seven products have obtained the orphan reward of two additional years of market exclusivity, the first one being in 2014. It notes that in some instances, companies voluntarily waived the orphan designation in order to make the product eligible for the SPC reward. "This may be explained by the fact that the SPC reward protects the entire product family of a specific compound across different therapeutic indications, while the orphan reward is limited to protecting the orphan use," the commission says. "Where medicines have both common and rare conditions, revenues from a 6 month SPC prolongation might be higher than from an additional two years market exclusivity in the orphan condition."

At this stage and without further studies, it is not possible to estimate the economic value of the orphan reward, based on a similar sample size to that of the SPC reward, given that most of the products are still under protection, the report says. "Therefore, it is not possible to analyse the actual impact of the loss of exclusivity on revenues."

PUMAS

Regarding PUMAs, only three such authorizations have been granted, according to the report. The main goal of a PUMA is to

stimulate research into existing compounds that are off-patent and/or to help transform known off-label use into an authorized use that is safer and better framed through the marketing authorization. Once approved, the PUMA provides the manufacturer with a ten-year period of marketing protection during which generic versions cannot be placed on the market.

The PUMA concept struggles with similar issues to those of any scheme that is meant to encourage companies to invest in additional research for known compounds that have been on the market for a long time (repurposing), the commission says. "Medicine developers fear that a PUMA will not necessarily prevent physicians from continuing to use competitor products with the same active ingredient but authorised for other indications off-label, at lower costs, nor substitution for cheaper forms at the level of pharmacies. Moreover, national health care payers are generally hesitant to agree a premium price for such products."

Other actions that the commission is planning in order to streamline the application and implementation of the Paediatric Regulation as a result of the new report include:

- providing additional transparency of new products authorized with pediatric indications;
- revisiting processes and expectations in the context of handling of applications for PIPs and if necessary adapting the corresponding commission guideline;
- exploring opportunities to discuss pediatric needs in an open and transparent dialogue involving all relevant stakeholders like academia, health care providers, patients/care givers, pediatric clinical trial networks, industry and regulators;
- delivering regular updates about development and trends in the pediatric medicines landscape in the EU; and
- fostering international cooperation and harmonization.

From the editors of Scrip Regulatory Affairs. Published online October 26, 2017

Australia To Bring Complex Stem Cell Therapies Within Regulatory Fold

VIBHA SHARMA vibha.sharma@informa.com

The Australian government is working on legislative changes to formally regulate some autologous cell and tissue products, including stem cell therapies, by requiring them to comply with quality and manufacturing standards prescribed by the Therapeutic Goods Administration. While some of the products will be regulated as biologicals, the level of regulation in all cases will be determined by the risk posed to patient safety.

By introducing formal regulations for such products, Australia will be in closer alignment with international regulators, such as those in the US and the EU, that have also developed respective frameworks to address global concerns regarding the direct-to-consumer advertising of unproven interventions to patients and the increasing complexity of treatments being offered, often for very serious illnesses. The US Food and Drug Administration announced in August that it is working on a new policy and enforcement efforts to ensure proper oversight of stem cell therapies and regenerative medicine. *(Also see "US FDA's Drug Seizures Seen As Most Significant Aspect Of Stem Cell Crackdown" - Pink Sheet, 6 Sep, 2017.)*

The TGA has not previously had any control over autologous human cell and tissue products because historically such products are viewed as an extension of medical practice. However, the government believes that some degree of oversight is now necessary.

New regulations will be drafted by the Office of Parliamentary Counsel over the coming months and submitted to the government for approval. The changes are expected to come into effect in early 2018, as a result of which autologous cell and tissue products subject to formal regulation would have to:

- be classified in accordance to their risk level;
- be included on the Australian Register for Therapeutic Goods;
- comply with the TGA's quality and manufacturing standards; and
- comply with adverse event reporting requirements and advertising controls.

Specifically, the proposed changes would result in regulatory exemptions being granted to only those autologous cell and tissue products that are manufactured and used in a hospital by a medical or dental practitioner, for a patient in the care of the same practitioner.

Regulation by the TGA, with exemptions from some requirements, is to be introduced for products that are minimally manipulated and are for homologous use only and manufactured and used outside a hospital by a medical or dental practitioner for a patient in the same practitioner's care.

Requirements of the TGA's biologicals framework would apply to products that are manufactured and used outside an accredited hospital, and are more than minimally manipulated or are for non-homologous use.

A transition period will be allowed to give affected manufacturers time to align with the new regulatory requirements. Detailed guidance on the new regulatory approach is currently being drafted. The TGA, for its part, will consult with stakeholders on the development of these documents in the coming months.

From the editors of Scrip Regulatory Affairs. Published online October 26, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Indivior Pharmaceuticals' buprenorphine subcutaneous injection for treatment of opioid dependence	Psychopharmacologic Drugs/Drug Safety and Risk Management	Oct. 31
Braeburn Pharmaceuticals' buprenorphine subcutaneous injection for treatment of opioid dependence	Psychopharmacologic Drugs/Drug Safety and Risk Management	Nov. 1
Clinical development plan for Pfizer's Staphylococcus aureus vaccine intended for pre-surgical prophylaxis in elective orthopedic surgical populations	Vaccines and Related Biological Products	Nov. 7
Bayer HealthCare Pharmaceuticals' ciprofloxacin inhalation powder for reduction of exacerbations in non-cystic fibrosis bronchiectasis adult patients (≥18 years of age) with respiratory bacterial pathogens	Antimicrobial Drugs	Nov. 16
Bulk drug substances nominated for inclusion on the Sec. 503A Bulks List and drug products nominated for inclusion on the list of drug products that present demonstrable difficulties for compounding under Sec. 503A and 503B ("Difficult to Compound List")	Pharmacy Compounding	Nov. 20-21
Discussion of patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for drugs intended to treat interstitial cystitis and bladder pain syndrome. Also discussion of whether bladder pain syndrome and interstitial cystitis reflect overlapping or different populations, and whether it is appropriate to assess efficacy in the same way for both conditions	Bone, Reproductive and Urologic Drugs	Dec. 7

Pink Sheet

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EDITORIAL OFFICE
52 Vanderbilt Avenue, 11th Floor
New York, NY 10017
phone 240-221-4500, fax 240-221-2561

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General Enquiries:

Jo Kirkpatrick | Tel: +44 (0) 20 7017 7180 | Email: jo.kirkpatrick@informa.com

Sponsorship and Table Booking Enquiries:

Chris Keeling | Tel: +44 (0) 20 3377 3183 | Mobile: +44 (0) 7917 647 859
Email: christopher.keeling@informa.com