Trump Slams FDA Regulations In Joint Session Of Congress
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President Trump offered an uplifting story about drug approvals during his Feb. 28 address at a joint session of Congress, but unfortunately for FDA, it was the villain in the piece, with “burdensome” agency restrictions becoming a key example in Trump’s criticism of government over-regulation.

Trump featured in the audience a rare disease survivor – 20-year-old Megan Crowley – who suffers from Pompe disease, an inherited disorder caused by the buildup of glycogen in the body’s cells. Crowley was diagnosed with the disease when she was 15 months old, although she was not expected to live past age five, the president said.

Megan’s father, John, founded Novazyme Pharmaceuticals Inc. to develop treatments for her. That company is now part of Sanofi’s Genzyme Corp., and John Crowley is the CEO of Amicus Therapeutics Inc.

Trump praised Megan’s story as a miracle, but added that FDA has stifled innovation to prevent more miracles like hers from occurring.

“But our slow and burdensome approval process at the Food and Drug Administration keeps too many advances, like the one that saved Megan’s life, from reaching those in need,” Trump said. “If we slash the restraints, not just at the FDA but across our government, then we will be blessed with far more miracles like Megan.”

The president echoed his previous comments about approval times he made to industry executives and representatives of the Pharmaceutical Research and Manufacturers of America (PhRMA) at a January meeting, where he said the approval process would become “a quick process,” and that his administration would be “changing a lot of the rules.” (Also see “Trump Promises Changes To ‘A Lot Of Rules’ At US FDA” - Pink Sheet, 31 Jan, 2017.)

Trump also touted his “one in, two out” executive order on regulations, as well as the federal hiring freeze. FDA, however, appears to have largely been spared from the executive order, (Also see “US FDA Likely Not ‘Significant’ , Could Be Mostly Spared From Trump’s Regulation-Slashing Order” - Pink Sheet, 10 Feb, 2017.) and has broad exemptions within the hiring freeze. (Also see “US FDA Commissioner Search: Pharma’s Preferred Candidate Is Gottlieb” - Pink Sheet, 5 Feb, 2017.)

Although Trump reiterated his sentiments on faster drug approval times and deregulation, he did not address any specific visions for reform at the agency. The president has not named a new commissioner for the agency yet, although Scott Gottlieb, a former deputy commissioner of the agency and a current American Enterprise Institute fellow, is believed to be the favorite. (Also see “US FDA’s Bipartisan Support May Offer Shelter From Political Winds, Former Chief Says” - Pink Sheet, 14 Feb, 2017.)

CONTINUED ON PAGE 4
The balance of power behind the prescribing decision is changing: payers are ever more in charge. That means that insight into how payers make decisions – how they evaluate drugs, one against another – will be crucial to any successful drug launch.

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Rare Disease OPEN-ing In PDUFA Possible For Drug Repurposing Advocates
http://bit.ly/2m3Kcgh
OPEN ACT would provide additional six months of exclusivity when existing drugs are approved for rare diseases; congressional debate over the measure could get bogged down in drug pricing issues.

Where Will It End? Lilly’s US Price Concessions Increase 30% In 2016
Industry-wide trend has some executives arguing the rebate system is unsustainable, as firms suggest PBMs are contributing to problem of high drug costs by their discount demands.

Pharma Attacked For ‘Playing The System’ Of EU Pediatric Rewards
http://bit.ly/2m3JJLi
As a public consultation comes to an end, French drug bulletin Prescrire says firms take advantage of incentives and pay only lip service to need for new medicines for children.

Ex-Pfizer Employee Overseeing Xeljanz Global Marketing Sued For Trade Secret Theft
Pfizer says its former global marketing director emailed and copied hundreds of documents on product launch plans and steps to obtain government approvals before leaving the company in January.

Biosimilar Litigation: Genentech Avastin Suit Tossed; Janssen Remicade Case Uncertain
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US court dismisses Genentech suit over Amgen’s patent dance moves; Janssen v. Celltrion trial is postponed as parties fight over Janssen’s standing to sue; and Amgen wants to bar AbbVie citizen petition filers from seeing its Amjevita information.
President Trump And Drug Pricing: Rhetorical Improvement But Uncertainty Remains

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First, the bad news: President Donald Trump isn’t dropping his promise to address prescription drug pricing as an early goal of his new Administration.

Somewhat predictably, Trump’s call for action on drug pricing during his address to a joint session of Congress February 28 was one of the few remarks that drew a bipartisan ovation. That underscores the challenge for industry when a Republican president espouses policies that have long had Democratic support.

Now the good news: Trump’s rhetoric was a long way from his pre-Inauguration remarks that the drug industry in the US is “getting away with murder.” It was also far gentler than the language he used in convening a meeting with pharma industry CEOs Jan. 31, when he called prices “astronomical.” (Also see “Carrots and Stick: Biopharma At The White House” - Pink Sheet, 31 Jan, 2017.)

Here is exactly what Trump said:

*We should implement legal reforms that protect patients and doctors from unnec-

essay costs that drive up the price of insurance and work to bring down the artificially high price of drugs and bring them down immediately.*

There are several reasons to view that as good news.

• First, the distinctly un-Trumpian language makes the line fairly unmemorable. While the overall speech was deliberately toned down from Trump’s usual colorful and bombastic style, it is hard to imagine that the drug pricing comment will stand out as a rallying cry for Trump’s base or anyone else.

• Second, the statement places the drug pricing response in a subsidiary position to the much broader and incredibly unsettled effort to repeal and replace the Affordable Care Act. The line above was the fourth point out of five in a list of principles offered to guide the effort. In other words, Trump did not call for action on drug pricing as a stand-alone agenda item, but rather...
as part of the overall health care effort—and as a small, almost forgettable part of that project.

- Third, and potentially most important, Trump’s language is vague enough to open up the possibility that he is calling for changes that the industry supports rather than action the industry opposes. The idea that prices are “artificially high” may just be a bland way to invoke concepts like reimportation or price negotiation. But it could also be an opening to “bring down prices” by focusing on the pharma industry’s argument that list prices are inflated by middlemen in the supply chain. Maybe cutting out that “artificial” inflation will be enough to satisfy the President.

It goes without saying that the industry would much prefer that a President not call out drug pricing at all during a prominent policy address. But it is hard to imagine a less-threatening turn of phrase than the one Trump used—all the more so given his prior remarks.

Now, if only the industry could get Trump to tone down his rhetoric on FDA. (Also see “Trump Slams FDA Regulations In Joint Session Of Congress” - Pink Sheet, 28 Feb, 2017.)

From the editors of the RPM Report. Published online March 1, 2017

MEDICAID DRUG FORMULARY IDEAS FLOATED, BUT US MANUFACTURERS ARE SKEPTICAL

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Lobbyists in the US are offering ideas for lowering prescription drug costs in Medicaid through the use of more restrictive formularies and rigorous price negotiation as Congress and the Administration work on a plan to refashion the program as part of the legislation to “repeal and replace” the Affordable Care Act.

The general idea being circulated is to allow programs to use formularies to more aggressively negotiate for rebates. Currently, all drugs must be covered if manufacturers participate in the Medicaid Drug Rebate Program (MDRP) and provide the statutory rebates.

The implication is that the new approach would supplant the MDRP and replace it with a system in which rebate amounts are not set by law but are negotiated between plans and manufacturers.

Under the law, the base rebate for branded drugs is 23.1% of the average manufacturers price or the best price offered in any market, whichever is lower. Manufacturers must also pay a supplemental rebate when prices increase faster than inflation. Although drugs cannot be excluded from coverage if manufacturers participate in the drug rebate program, states and managed care organizations can, and often do, apply utilization management tools like prior authorization or drug utilization reviews to restrict access.

The idea of a market-based solution to lowering prices is appealing to manufacturers. However, they are concerned that legislators will not be willing to give up the Medicaid rebate money currently required under the MDRP. As a result, manufacturers worry they might find themselves in a situation where they are both liable for existing rebates and subject to further concessions to ensure favor-
Manufacturers have tried to promote value-based contracts with Medicaid plans but have not gained much traction, Sarraille said.

is worth considering for the Medicaid enrollees covered by MCOs. The proposal would not apply to fee-for-service Medicaid.

However, “the key trade-off here is that [Medicaid plans] would not have to cover” all drugs. “Just like in Medicare Advantage, it would be something like two drugs in every category or class and that means some drugs are not going to get covered,” he pointed out.

Myers also suggested the new system could incorporate risk sharing contracts between plans and manufacturers. However, he acknowledged there are regulatory obstacles standing in the way, including federal anti-kickback rules and FDA restrictions on pre-approval discussion. (Also see “Value-Based Contracts: Relief From Regulatory Barriers In Sight?” - Pink Sheet, 13 Feb, 2017.)

WILL GOVERNMENT BE WILLING TO FORGO GUARANTEED REBATES?

In response, Janssen Inc. Senior Director for Government Contracts Michael Hepburn acknowledged “we would much prefer this model because from the manufacturer’s perspective, on the Medicaid side, we are already saddled with the 23.1% rebate, or for a drug that’s been on the market for a while, it could be a 50%, 60% or 70% rebate” with the price inflation penalty. “So it’s very difficult.”

However, he pointed out, “some of the struggle is that it’s hard to take money away from those rebate payments and sell that [idea] to the states and feds.”

“It’s quite possible what [legislators] are going to ultimately think about is adding some room for states, and by extension MCOs, to exercise negotiation in addition to the minimum rebate percentages as they exist,” Sidley Austin Partner William Sarraille agreed.

“I think people are skeptical the carrot you are offering” will be available, he told Myers.

Sarraille also suggested that manufacturers have tried to promote the idea of value-based contracts with Medicaid plans but have not gained much traction.

“A lot of [manufacturers] in this room have engaged with both state Medicaid programs and Medicaid managed care plans about value-based initiatives, and I think there is a certain cynicism here as to what the real level of interest is. … It is very difficult to get plans to focus on more than a very few value-based initiatives at any one time,” he said.

Myers acknowledged that Medicaidplans have trouble thinking through a value-based purchasing arrangements for lots of different drugs because they don’t have to.” Anti-kickback concerns are also a major factor, he pointed out.

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able formulary access.
Congress is considering transforming the federal government’s contribution to Medicaid programs into a block grant or creating a per capita cap, which some analysts believe could significantly reduce funding for the program. Congress has not specifically addressed drug cost controls in those proposals, which offers stakeholders an opportunity to shape policy.

The National Association of Medicaid Directors proposed among its 2017 legislative priorities that congress provide authority for “new purchasing and reimbursement strategies for Medicaid’s prescription drug benefit, including flexibility to exclude some FDA-approved drugs from coverage.”

The Pharmaceutical Care Management Association, which represents pharmacy benefit managers, is also advocating for controlling prices through enhanced formulary negotiation authority and hopes PBMs would play an important role in the new system. (Also see “Part Of The Solution? PBMs See Opportunities In Medicaid Reform” - Pink Sheet, 15 Feb, 2017.)

Pharmacy benefit managers such as Express Scripts Holding Co. currently operate in the Medicaid space but could improve cost control with additional formulary tools in areas with rapidly growing spending, such as specialty drugs. Increases in the unit cost of specialty drugs rose sharply in 2016 (see box).

Medicaid Health Plans of America, which represents Medicaid managed care organizations, is also looking at alternatives to the existing drug rebate program, President and CEO Jeff Myers told the Government Programs Summit in Arlington, Va. Feb. 28. Seventy-three percent of Medicaid enrollees are covered by managed care organizations.

He suggested that a model based on the way Medicare Advantage drug plans use formularies to negotiate with manufacturers...
FDA and industry have serious concerns with a proposed six-month priority review pathway for generic drugs offered in recent legislation, arguing it may not actually get generics to market faster.

Both industry and agency agree with the bill’s ultimate goal, pushing more generic competition to the market faster. But during a March 2 House Energy and Commerce Committee Health Subcommittee hearing, they implied that shortening the review time may not be the best way to achieve it.

The Lower Drug Costs Through Competition Act (H.R. 749), sponsored by Rep. Kurt Schrader, D-Ore., and Gus Bilirakis, R-Fla., would create a six-month priority review pathway for ANDAs for drugs with only one sponsor marketing them already, products on FDA’s drug shortage list, or possibly first generics. Once approved, those sponsors also could receive a priority review voucher. (Also see “Drug Pricing Bill May Make Six-Month ANDA Review Slower Than Eight-Month Review” - Pink Sheet, 2 Feb, 2017.)

During the hearing, which also addressed the generic drug and biosimilar user fee re-authorizations, Center for Drug Evaluation and Research Director Janet Woodcock said it would be difficult to make priority ANDA reviews as short as six months. After the hearing, she also said that she was concerned about the goal of the idea in the context of GDUFA’s older sister, the prescription drug user fee program.

And while ANDA sponsors think the legislation’s six-month review deadline may be overly aggressive, they think its approach to restricted distribution programs is overly timid. (See related story, p. 8)

Woodcock would not comment on the bill specifically, but said FDA and industry agreed to lengthen review times as part of the previous PDUFA reauthorization in order to speed up NDA approvals, i.e. increase first-cycle clearances.

Indeed, the idea to add two additional months to NDA reviews to allow mid-review application corrections seems to have worked as intended. (Also see “Buying Time: Industry Sacrifices Early To Gain Later With PDUFA V Review Model” - Pink Sheet, 1 Oct, 2012.)

FDA appears to be embracing the same theory to boost the ANDA first-cycle approval rate and reminded lawmakers that it may simply take time for the approval speed to manifest. The rate now stands at about 9%, Woodcock said during the hearing. But she said during GDUFA II, the agency would like to increase the rate to 20%-25%.

“The PDUFA program over the 20 years of operating has brought the first-cycle drug approval up to well over 80%. ... But it wasn’t that way at the beginning,” Woodcock said. Currently, many ANDAs require four review cycles before approval. (Also see “Generic Drug First-Cycle Approval Rates Lagging Under GDUFA I” - Pink Sheet, 25 Oct, 2016.)

In order to increase the likelihood of a first-cycle approval, GDUFA II also includes pre-submission meetings for sponsors of complex generic applications. (Also see “Complex ANDAs To Be Allowed Pre-Submission Product Meetings” - Pink Sheet, 24 Oct, 2016.)

LIKE THE GOAL, NOT THE VEHICLE

David Gaugh, senior VP of sciences and regulatory affairs for the Association for Accessible Medicines (formerly the Generic Pharmaceutical Association), said after the hearing that shortening priority reviews, even for only a portion of incoming ANDAs, would be demonstrably difficult. He also said parts of the GDUFA II agreement could be put at risk by the six-month priority review idea. The agreement includes an eight-month priority review pathway. (Also see “ANDAs Can Get Priority, Eight-Month Reviews Under User Fee Deal” - Pink Sheet, 24 Sep, 2016.)

Gaugh said that AAM applauds the goal, but has made its position clear to House
members. That may have been why neither Woodcock nor Gaugh, who both testified at the hearing, were specifically asked about the six-month pathway.

Even though FDA seems to have fought off one attempt at altering its review practices, others likely will emerge as the user fee package takes shape in the coming months, especially if it applies to drug pricing. (Also see “Obamacare Repeal May Be Delaying User Fee Bill, Rep. DeGette Says” - Pink Sheet, 8 Feb, 2017.)

LITTLE TIME FOR ANDA CORRECTIONS WITH SHORTER PRIORITY REVIEW

FDA also pointed to logistical challenges that would hinder a faster priority review pathway from speeding up generic approvals. Woodcock said six months likely is not enough time to schedule and conduct a facility inspection, especially if it is overseas.

“Generics typically have many more establishments in their application than a brand application has and they might be all over the world,” she said. “We need to have enough time in which to do inspections, in different countries if necessary.”

The Government Accountability Office has flagged FDA for its problems conducting foreign inspections, saying recently that it should take more advantage of its foreign offices to complete the facility visits. (Also see “US FDA’s Foreign Inspection Agenda: Visit The 1,000 Facilities It’s Never Seen” - Pink Sheet, 17 Jan, 2017.)

Woodcock also said in written testimony that work with sponsors to make mid-review corrections to applications would be limited with a shorter pathway. She said cutting two months off a priority review “would wind down work just when it is gaining momentum. … Applicants would not have time to make corrections and thus get their ANDAs approved,” she stated. “To resolve outstanding issues, an additional cycle of review would be necessary. Approval would be delayed for at least six to 10 more months, depending on how quickly the applicant could develop an amendment.”

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REMS Reform Seems Distant Goal For Generics After Limited Support At US House Hearing

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Imagine this scene: Republicans call a hearing to discuss how a federal agency handles a regulated industry. Company executives and government bureaucrats are present. Then the elected representatives from the party of small government don’t tee up any questions for industry to offer its preferred solutions to the problems it sees with current regulations.

That’s the situation the generic industry found itself in during a March 2 hearing by House Energy & Commerce Subcommittee on Health, and it suggests that reforms to Risk Evaluation and Mitigation Strategies (REMS) are long way off, if Republican interest in the issue at is any indication.

Although a few Democratic representatives raised the issue, the REMS barrier did not gain any traction among Republicans, who did not ask any questions to witnesses about the topic.

Committee members at the hearing discussed renewal of the ANDA and biosimilar user fee programs as well as the Lower Drug Costs Through Competition Act (H.R. 749), sponsored by Rep. Kurt Schrader, D-Ore., and Gus Bilirakis, R-Fla., which has a requirement for the Government Accountability Office to submit a review on the effectiveness of the REMS program to Congress by May 1, 2018.

However, David Gaugh, senior vice president for sciences and regulatory affairs at the Association for Affordable Medicines, formerly known as the Generic Pharmaceutical Association (GPhA), contended that another study is not necessary.

“We have been looking at REMS since I was at the GDUFA [Generic Drug User Fee Act] table in 2012, and working on solutions for that,” Gaugh said in response to a question from Rep. Gene Green, D-Texas, about barriers to generic entry. “And we’ve had solutions that have been presented even in the last six months that never quite make it into the bill. And so REMS is one of the main indicators that prevents generic products from coming to market because we can’t get the product to be able to develop the generic of the innovator.

“When you try to buy or try to purchase [a drug with a REMS], since you are not a qualified patient, you do not get access to those drugs.”

GPhA previously sponsored a study that found that $5.4 billion in potential savings could be realized annually if generic versions of 40 medicines were allowed to compete in the marketplace. If the studied drugs were fully genericized, annual sales would be about $2.2 billion, a 71% decrease from the current sales estimates. (Also see “REMS And Generics: GPhA Needs Legislation, Continues Education” - Pink Sheet, 4 Aug, 2014.)

The generics industry also has doubts about the main thrust of the Bilirakis/Schrader legislation – a six-month review clock for priority ANDAs.

For REMS, Allan Coukell, senior director of health programs at the Pew Charitable Trusts, noted while that not high in num-
GENERIC DRUGS

ber, there are some costly drugs with a restrictive distribution that would benefit the public by having generic competition.

“Making sure that there is a pathway for generic versions of those drugs and non-REMS drugs that have restricted distribution could be meaningful,” Coukell said.

Center for Drug Evaluation and Research Janet Woodcock affirmed in an earlier panel at the hearing that the misuse of REMS by brand name drugmakers has indeed been a hindrance to getting generics to market.

Although FDA can send a letter to the brand name drug company to confirm that the generic maker’s use of the product is appropriate following a review of protocols, the agency cannot compel the innovator to provide its drug for bioequivalence studies.

“I know it is a problem that we struggle with a lot, and that the companies struggle with, and it has delayed the availability of generics,” Woodcock said in response to a question from Rep. Frank Pallone, D-N.J. But FDA did not call on Congress to act, illustrating another conundrum for the generic industry. When asked by Pallone whether legislation is the solution to the issue, Woodcock responded “I don’t know the answer to that.”

Any congressional action on the issue would require Republican support, however, given the party’s majority status in both houses. However, GOP members appeared uninterested in the issue.

HEARING STILL CREATES DEBATE

As an alternative to Bilirakis and Schrader’s Lower Drug Costs Through Competition Act, Bruce Leicher, general counsel at Momenta Pharmaceuticals Inc. and chair of the Biosimilars Council, instead touted the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act as a solution to REMS abuse.

The CREATES Act – introduced in the previous Congress, but not yet formally offered in the new one – would provide a legal remedy for generic companies that feel a brand sponsor is using a REMS or other restricted distribution system to prevent them from obtaining samples for testing. (Also see “Shkreli Fallout Continues: PhRMA Seems To Soften Stance On REMS Legislation” - Pink Sheet, 22 Jun, 2016.)

Such a measure would help companies to get samples of Daraprim (pyrimethamine) from Turing Pharmaceuticals AG, which had created a controlled distribution program for the antiparasitic for which former CEO Martin Shkreli raised the price by 5,000%, the panelists said. It is unknown, however, whether companies have ever actually attempted to develop a generic of Daraprim.

The Pharmaceutical Research and Manufacturers of America (PhRMA) has been critical of such legislation, describing REMS as “a critical regulatory tool for protecting patient safety.” (Also see “REMS Abuse Legislation: GPhA and PhRMA Set To Battle Again” - Pink Sheet, 15 Jun, 2016.)

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EU and the US officials have finally signed an agreement that allows their drug regulators to rely on each other’s good manufacturing practice inspections conducted within their respective territories.

The agreement represents the culmination of nearly three years of EU and US co-operation under the Mutual Reliance Initiative and will allow the EU drug inspectors and the US Food and Drug Administration to rely upon information from drug inspections conducted within each other’s borders. (Also see “US-EU Mutual Reliance On Drug Facility Inspections Nears Reality” - Pink Sheet, 24 Mar, 2016.)

The agreement, signed March 1 by European Commissioner for Trade Cecilia Malmström, had been signed six weeks earlier by the Obama administration’s US trade representative, Michael B.G. Froman, on Jan. 19, the day before Donald Trump assumed the US presidency. FDA told the Pink Sheet that the Trump administration’s transition team for FDA and the Health and Human Services Department “were fully briefed on it before its entry into force.”

The deal means the need for an EU authority to inspect a site located in the US, or vice versa, will in the future be limited to “exceptional circumstances,” the European Medicines Agency said in a statement. In the EU, inspections of manufacturing sites are carried out by EU member states national competent authorities and EMA plays an important role in coordinating these activities.

EMA says that the agreement will allow both EU inspectors and FDA to make better use of their inspection resources and focus other parts of the world where active pharmaceutical ingredients and medicines for the EU or US markets are manufactured. It says around 40% of finished medicines marketed in the EU come from overseas and 80% of API manufacturers for medicines available in the EU are located outside the union.

FDA associate commissioner for global regulatory policy Dara Corrigan said the agreement would help avoid duplication of drug inspections, lower inspection costs and enable both EU and US regulators to devote more resources to other parts of the world where there may be greater risk.

The agreement is expected to improve the EU’s ability to identify and address problems at factories before they become a public health risk, and also reduce the administrative burdens and costs facing pharmaceutical manufacturers, including smaller producers, the European Commission said on its website.

US YET TO INSPECT ALL EU MEMBER STATES

EMA said the agreement was underpinned by robust evidence on both sides of the Atlantic that the EU and the US had “comparable” regulatory and procedural frameworks for inspections of drug manufacturers.
Since May 2014, FDA and the EU have been collaborating to evaluate how they each inspect drug manufacturers and assessing the risk and benefits of mutual recognition of drug inspections. FDA said it was invited to observe the EU’s Joint Audit Programme, in which two EU nations audit the regulatory authority (inspectorate) of another EU country.

FDA first observed the audit of Sweden’s inspectorate by auditors from the UK and Norway. Since then, FDA has observed 13 additional audits of human medicine inspectorates in Greece, Germany, Croatia, the UK, the Czech Republic, Hungary, Italy, Austria, Lithuania, Romania, Malta, Spain and Estonia. More audit observations are planned through 2017.

FDA told the Pink Sheet that the UK’s Brexit vote won’t impact the agency’s relationship with its UK counterparts. “Once the UK finalizes its departure from the EU, FDA and the UK will re-examine existing commitments and, if necessary, renegotiate any existing agreements,” the agency said.

The agreement is an amended annex to the EU-US MRA which was signed in 1998, but is not yet implemented. The EMA explained that many provisions of the agreement entered into force March 2, the day after Malmstrom signed it, while others will enter into force on Nov. 1, 2017. By that date, it said, the EU will have completed its assessment of FDA and FDA is expected to have completed its assessment of at least eight EU member states. The FDA’s assessment will gradually be expanded to cover all member states by July 15, 2019.

FDA and EU inspectorates will retain their authority after Nov. 1 to inspect manufacturing facilities in each other’s territories, but the agreement says that after Nov. 1, this “should be an exception from the normal practice.” EMA and FDA both told the Pink Sheet that their intent is to rely on each other’s surveillance inspections in their respective regions.

The agreement also covers pre-approval and for-cause inspections, allowing US and EU authorities to request them and, if declined, to conduct them themselves, with the host authority joining if it wants.

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**First Approvals Under EMA’s Adaptive Pathways May Be Just A Few Years Away**

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The first drugs to be developed under the European Medicines Agency’s much talked about adaptive pathways concept for getting drugs for high unmet medical needs to patients faster could be just a few years away from approval.

Most of the marketing authorizations are likely to take place “in the early-mid 2020s” an EMA spokesperson said of the investigational drugs that were accepted on the agency’s adaptive pathways pilot project that ran between March 2014 and August 2016. “We do not expect marketing authorizations before 2019,” the spokesperson said.

The concept of adaptive pathways, which the EMA is still fine tuning, has generated considerable interest, as well as controversy, over the past few years. Many are waiting to see whether it does in fact cut drug development times and whether regulatory safety standards will be maintained. Investigational medicines accepted on the pilot were in the early stage of clinical development, which usually means prior to the initiation of confirmatory studies (i.e., during or before Phase II).

It is not clear how many of the drugs in the pilot might be approved by mid-2020 or who their sponsors are, as companies discussed their applications with the EMA in a “safe harbor” environment. Only a few applicants such as bluebird bio and Immunocore have publicized the fact that they had been accepted on the pilot.

By the end of the pilot, 20 of the 62 applications submitted had been accepted to take part in a short Stage I meeting with the regulators. Of the 20 applications, 18 had been selected for Stage II – six of these applications had progressed to receive scientific advice that the EMA offers companies in parallel with health technology assessment (HTA) bodies, and one application had received formal scientific advice from just the agency. The EMA said it was not specifically tracking the applications that have not progressed.

Some applicants have now reached the stage where they are conducting their studies, the EMA spokesperson told the Pink Sheet. Also, the agency is still accepting applications for the adaptive pathways concept. (Also see “Adaptive Pathways: Companies Advised To Consider Hurdles As EMA Accepts More Applications” - Pink Sheet, 5 Aug, 2016.)

For new applications for adaptive pathways, the agency offers an additional pre-submission meeting to discuss ideas and
By the end of the pilot, 20 of the 62 applications submitted had been accepted for a short Stage I meeting with the regulators. Of those, 18 had been selected for Stage II.

Finalization of protocols that will be the subject of parallel scientific advice with HTA bodies. “If companies already have clear ideas of what they want to do, the usefulness of this meeting is limited and they are invited to go for a normal HTA/scientific advice procedure,” the EMA spokesperson said. “So far we have had two additional pre-submission meetings, with two others being considered.”

GROWING DEBATE

The adaptive pathways concept has been the subject of growing debate since 2010, when it was featured in the EMA’s “road map” to 2015.

It aims to improve patients’ access to medicines in cases of high unmet medical need by enabling a drug to be approved earlier than usual based on limited data for restricted populations where its benefit-risk balance could be favorable, and then using real-world data to support its wider use. It also seeks to involve HTA bodies early on in development to increase the chance that a drug will be recommended for payment and ultimately covered by national healthcare systems.

Advantages for applicants whose product meets the adaptive pathways criteria may include earlier access to market, improved focus of research leading to more efficient use of internal resources, and a higher probability of satisfactory reimbursement after marketing authorization.

Adaptive pathways detractors, on the other hand, warn that the approach might result in the EMA dropping its standards since it would be authorizing drugs based on limited evidence. Concerns have also been raised over a lack of clarification on how real-world data can be used to draw reliable conclusions about the benefits and risks of a drug. (Also see “EMA Defends Adaptive Pathways Against Fresh Attack Following Pilot Report” - Pink Sheet, 11 Aug, 2016.)

The EMA has repeatedly maintained that the same standards of benefit-risk assessment will be maintained under an adaptive pathways approach.

Adaptive pathways is not a new route of marketing authorization, the agency points out. Rather, it makes use of existing regulatory tools in a more efficient way. Medicines are still expected to be authorized through the existing legal routes and to benefit from incentives (such as orphan designation) that are already in place. “The difference is in the way medicines development will be planned to better meet the needs of patients with serious conditions for whom there may be no suitable treatments,” the agency explained in the recently-published report on its December 2016 adaptive pathways workshop.

The workshop, which was organized by the EMA and the European Commission, was designed to tackle important questions arising from the adaptive pathways pilot, including how best to address patients’ needs and expectations; how to generate appropriate data to aid medicines evaluation; and how to ensure that high standards for approval in the EU continue to be met. It took place in London and was attended by over 170 delegates, with 155 others logging in remotely.

The workshop report highlighted, for example, how adaptive pathways might provide improvements over the existing conditional marketing authorization (CMA) procedure, both of which use some of the same approaches, including a focus on unmet needs and small patient populations.

“The problem is that many conditional authorisations have been the result of late requests by applicants during EMA evaluations when it had already become clear that a standard authorisation or a broader indication would not be granted,” the report said. Furthermore, the data sets used to approve CMAs may differ from those normally required by HTA bodies in their assessments, a situation that could delay or prevent medicine reimbursement by national healthcare systems.

“The adaptive pathways concept has the advantage of being planned in advance, with regulators and HTA bodies working with companies early in development to determine which data can be acceptable and to allow for appropriate health technology assessment according to national requirements,” the report explained. “It may not necessarily result in faster approval, but it could lead to a more efficient use of data and resources to meet the needs of the widest number of stakeholders.”

The report said that the EMA and the commission were taking stock of the different views expressed on the adaptive pathways concept and the lessons learnt from the pilot “to determine ways to integrate proposals and address concerns within the existing regulatory system.”

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EMA's Post-Brexit Home ‘Could Be Decided This Year’

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A decision on where to relocate the European Medicines Agency following the UK’s decision to leave the EU could be taken sometime during the summer or the second half of this year, according to former Novo Nordisk CEO Lars Rebien Sørensen, who is leading Denmark's bid to bring the agency to the country’s capital, Copenhagen.

Sørensen, who was asked by prime minister Lars Løkke Rasmussen to be the ambassador for Denmark’s candidacy, says that it is “of the utmost importance” to find a location for the EMA as quickly as possible before the decision-making process gets tangled up in the wider Brexit negotiations.

The currently London-based EMA is already losing some professional staff and “there is a concern that a dragged out process will continue to bleed staff from the EMA to the point where one can fear that the functionality of the agency could be hampered over time,” Sørensen said in an interview with the Pink Sheet.

The formal bidding process for the EMA will not begin until the UK government has triggered Article 50 to kick off negotiations over its exit terms and its future relationship with the EU, although several member states have already thrown their hats into the ring. They include Denmark, France, Ireland, Italy, the Netherlands, Spain, Sweden and Portugal, and, according to a question and answer document published by the Dutch government last month, Austria, Hungary and Malta have also expressed an interest.

Denmark has produced a brochure describing its benefits in areas like transport links, infrastructure, a strong life sciences sector, schooling, housing, and cultural factors. (Also see “‘Virtually Bribery And Corruption Free’ Denmark With Its Clean Canals Says ‘Give Us EMA’” - Pink Sheet, 10 Feb, 2017.) Sørensen, who stepped down as Novo Nordisk CEO last month after 16 years in the job, said that the Danish government believes Copenhagen fits the bill nicely, and “I was given the brief to take that to the decision-makers’ attention.”

THE BIDDING CRITERIA

As part of this brief, Sørensen recently paid a visit to Brussels to speak with representatives of the European Commission and other EU bodies, as well as associations representing industry, patients and pharmacists, about the bid process and the criteria that the suitor countries will have to meet.

As far as Sørensen knows, the Commission hasn’t yet produced a formal list of criteria, but he expects it will do soon, and that they will be based firmly on input from the EMA. “I know criteria have been suggested by EMA and by EFPIA [the European pharmaceutical industry federation],” he said. “It wouldn’t take long to develop them”.

While the EMA will not take the final decision on the location, the former Novo Nordisk executive said it was important that the agency “describes what are the important features for a well-functioning EMA, that these are included in the criteria, and then that the criteria are publicized so that the member states can decide whether to participate in the relocation or not.” Two documents relating to Brexit that the EMA has produced are available on the EMA’s website.

Sørensen also feels that the member states themselves should not have a role in choosing the criteria, because “they would immediately be seen as being biased. We would actually prefer that the European Commission, the EMA, industry associations, patient
Lars Rebien Sørensen, Denmark’s ambassador for the country’s bid to host the EMA post-Brexit, is touring selected EU member states with a view to building up support for a rapid bidding and selection process – and for its own candidacy.

associations and whoever else in civil society is dependent on the functioning of the EMA should be part of defining those criteria.”

Once the criteria are published, a deadline will be set for countries to submit their bids, after which they will be evaluated by the Commission as regards their suitability, “and then a decision will be taken by the Council,” Sørensen said. This will probably be the European Council, which consists of EU heads of state/government.

And if all the bidding countries meet all the criteria? “At the end of the day it is a political decision as to where you place it,” Sørensen said. “There are all kinds of considerations, a history of having agencies, countries’ reputation for good governance, all kinds of evaluations could come into play from a political perspective.”

Sørensen said a decision could be made “as early as summer, or in the second half of the year, to be more realistic”. He added: “If it drags out, our concern is that it gets entangled with the general Brexit process, where there are lots of issues to be dealt with and one can imagine that that will lead to some horse-trading at the end of the day between Britain and the EU, but also among the individual EU countries in adopting an agreement with Britain.”

The agency might then be “swirled into that decision-making which would be very unfortunate given the importance of it.”

BUILDING UP NATIONAL REGULATOR

Partly for this reason, the Danish Medicines Agency has set about strengthening and expanding its regulatory expertise. “The expectation is that they will be expanding in the next couple of years prior to a possible relocation of the EMA,” according to Sørensen, who added that Denmark has a strong academic life science sector.

Denmark also has “a strong industry, much like Britain, not exactly at the same scale of course, but for historic reasons we have an unusually large pharmaceutical industry in Denmark.”

The country is also part of the Medicon Valley life sciences hub, which is shared between Copenhagen and southern part of Sweden. “So we think there is an ecosystem here from which EMA will be able to recruit, but where people from other parts of Europe would also find it interesting to relocate to work for the EMA,” Sørensen said.

And what if Denmark doesn’t win the EMA? “This expansion is being done with a view to prepare the Danish medicines agency [for hosting the EMA] but also because of anticipation that the Danish agency will be playing a larger role going forward in approvals of drugs and monitoring drug safety in the European scene,” he remarked.

In the meantime, Denmark isn’t sitting on its hands. Sørensen is touring selected EU member states with a view to building up support for a rapid bidding and selection process – and for its own candidacy.

“We are visiting some countries that we believe will not necessarily be bidding themselves, to try to rally some support both for the process but, secondary to that, for the Copenhagen bid,” he said. “I would suspect the other countries will be doing the same, this is part of normal courtship and diplomacy.” Sørensen declined to identify the countries Denmark would be visiting.

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Bayer CEO On Europe’s ‘Identity Crisis’

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Bayer AG CEO Werner Baumann outlined ambitious 2017 goals for the German big pharma during its Feb. 22 annual results conference, but he also said success for the wider biopharma industry is highly dependent on the fluctuating social and political environment in Europe and across the pond in the US.

Bayer's chief exec vowed to increase the firm’s €4.4bn R&D budget in 2017 as the company continues to push late-stage drug candidates towards the market, such as its Phase III prostate cancer product, BAY 1841788. However, he noted that high investment in R&D is associated with an increasing level of risk because of unreliable market conditions in Europe and the US.

Baumann highlighted two key concerns that could impact innovation for Bayer and the wider pharma sector in 2017. Firstly, he said Europe is experiencing an “identity crisis, with centrifugal forces increasing.” In light of the UK voting to leave the EU, Baumann said that other EU countries need to “inject new strength into the European ideal.”

“Given the skepticism of many EU citizens about the institutions in Brussels, we can’t simply carry on as before. The European Union will have to consider reform if it is to remain attractive in the long term,” he said. “We all need a Europe that is flourishing and fit for the future.”

Bayer’s chief is also pushing for a “soft Brexit” with as few social effects on the EU as possible. “Barriers to free trade would ultimately harm everyone,” he said.

In light of the UK voting to leave the EU, Baumann said that other EU countries need to “inject new strength into the European ideal.”

‘EMOTIONAL POLITICS’

Baumann, who took over as CEO of Bayer in May 2016 from departing chief Dr. Marijn Dekkers, also told the conference that objective political debate can no longer be expected. Hinting at situations in the US surrounding “fake news” claims from President Donald Trump and the use of “alternative facts” by members of the new Trump administration, Baumann said a profound change in the culture of political discourse is being experienced. “Emotions are increasingly the substitute for facts,” he said, adding that decisions are no longer based primarily on rational reasoning.

“It has made politics unpredictable – which is a severe handicap, especially for innovative companies like Bayer that have to plan and invest on a long-term basis,” he said.

At home Bayer is advocating for the introduction of a European innovation principle for examining the effects that all new laws might have on industry’s innovation capability. Baumann said that such an innovation principle is currently being discussed by industry associations across Europe. “We are making good progress arguing this case [to the European Commission],” he said.

Innovation as a political and legal principle was included in a document issued by the commission in June 2016. The commission said an innovation principle would focus on ensuring that the impact of a political decision on innovation is fully assessed, whenever policy is being made. Discussion around this topic are continuing.

BREXIT QUALMS

Concerning Brexit talks, Baumann said that Bayer – which has operations in Reading, England – is not being directly affected yet by the UK’s decision to leave the EU. “Frankly it is just too early [to tell], we do not know what the British regulations will look like. There is going to be a transition period of a few years before we might see any effects on our business. So far we have experienced no direct effects,” Baumann said.

Looking ahead though, Bayer’s leader said possible barriers to accessing the best talent because of new travel or visa laws implemented as part of Brexit negotiations are worrisome. He highlighted this as one of the drug maker’s biggest concerns, alongside potential and unknown regulation changes.

BAYER 2017 FINANCIAL FORECAST


‘From the editors of Scrip Regulatory Affairs. Published online February 24, 2017

Bayer execs in Leverkusen (l-r): Johannes Dietsch, Werner Baumann, Hartmut Klusik and Michael Preuss
A new wide-ranging circular issued on Feb. 9 by China's Cabinet, the State Council, outlines a number of fundamental policy changes, including the allowance of substitution of original branded but genericized drugs with high-quality, bioequivalent domestically manufactured generics, which will also be prioritized in hospital procurement processes.

Not only will local generics be interchangeable for original brands, the generics themselves will also face less competition in simplified public tenders. For example, only the first three domestic makers of the same generic product to pass bioequivalence testing will be able to participate in the tender, to the exclusion of other companies.

The general policy principles outlined in the document, “Opinions on Further Reforming Drug Manufacturing, Distribution and Usage”, are a new sign that Chinese regulators are looking to bring more pressure to bear on drug prices, industry experts say. (Click here to see the Circular – Chinese language.)

“From granting accelerated approvals to generics to now providing financial incentives, the message is clear - the government wants to increase generic shares, via both prices and volume,” Katherine Wang, a partner at international law firm Ropes & Gray’s Shanghai office, told Pink Sheet.

“Circular No. 13 reinforces the government’s determination to expedite approvals for new drugs and urges generics to pass quality consistency tests,” she added in a Feb. 20 alert.

COMPARATIVE PRICE SYSTEM

Incentives aside, the government is also poised to use more direct pressure to reign in drug prices. The State Council circular requires prices of new drugs and generics to not exceed those in the country of origin or China’s surrounding countries. Previously, Chinese regulators have usually required drug prices not to exceed prices in Hong Kong, Macao, Taiwan, and Japan.

Although the new document didn’t give details, the new list could potentially include India and Southeast Asian nations where drug prices are often lower, legal experts pointed out. The China FDA has been tasked with setting up a database of relevant ex-factory prices to monitor compliance.

“That could potentially bring more pressure to patented drugs, including offering volumes [in exchange for price concessions],” Wang pointed out.

In other moves enshrined in the circular, public hospitals will be expected to rationalize medicine use to control costs, and a pilot marketing authorization holder (MAH) scheme will be extended and potentially applied to both innovative new drugs and high-quality generics if they are developed or produced locally, again favoring local generic producers.

The MAH scheme, rolled out in 10 provinces in May 2016, enables domestic drug R&D institutions and individuals to apply for and hold drug product licenses, and the eligible parties can fully outsource manufacturing activities to contract producers. (Also see “Authorization Holder Scheme To Shake Up China R&D, Drug Production” - Pink Sheet, 8 Nov, 2015.)

PRICE DILEMMA?

However, the CFDA itself may have its own dilemma to deal with under the planned changes, whereby it is planning to seek price commitments from manufacturers of both patented and off-patent drugs at the time of applying for marketing authorization.

This may be difficult “particularly considering that the CFDA is not authorized by law to condition drug approval on price commitment,” noted partners Lei Li and Chen Yang at the Beijing office of another global law firm, Sidley Austin, in a Feb. 14 note.

Some details also need further outlining, they added, such as “whether companies will be prohibited to increase their drug prices after launch and whether companies will be allowed to adjust drug prices in China after launch when prices in overseas markets have changed.”

Since early 2016, China’s National Health and Family Planning Commission (NHFPC) has initiated national drug price negotiations, which have held out the promise of a larger volume market share in return for price cuts for some high-priced oncology and other drugs, but the volume uptake has in fact been mostly slow. (Also see “Deep China Price Cuts Reveal Complex Considerations” - Scrip, 23 May, 2016.)

Regulators are now requesting more incentives to participate, including leveraging public payers to offer timely reimbursement to both new and off-patented drugs, although volumes may still be used to bring down prices in collective tendering processes.

CL OVERHANG

Another renewed overhang to innovative companies in the new circular is that of compulsory licenses (CLs). Although China has yet to grant any CLs, the threat is ever-present and has been emphasized in recent years.

In the latest document, the government said it won’t hesitate in using CLs for any patented drug to force patient access to selected products. “Compulsory licenses can be granted and enforced for any patented drugs that prevent or treat critical illness," the Feb. 9
Mexico’s COFEPRIS: A Friend Or Foe To Industry?

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Mexico’s drug regulator, the Federal Commission for the Protection against Sanitary Risk (COFEPRIS), has been known across the pharmaceutical industry to be an agency of extensive red tape. The red tape itself, however, along with other factors, have turned Mexico into a growing market for pharmaceuticals in spite of the burdens companies may face, an expert says.

There are some barriers that drugmakers doing business in Mexico simply will not be able to avoid, José Alberto Campos-Vargas, a partner at the Mexican law firm Sánchez Devanny, tells the Pink Sheet in an interview.

For example, companies filing for marketing authorization for a drug must have all documents and information submitted to COFEPRIS translated to Spanish by an authorized translator.

When filing for a marketing authorization, all documents and information that is submitted with COFEPRIS must be translated to Spanish by an authorized translator. This includes all information related to the product, as well as all the legal documents such as agreements and licenses.

There are even certain cases where only individuals authorized by the company can file documents with COFEPRIS. When dealing with other agencies, companies can simply send a messenger to deliver documents. COFEPRIS, however, requires that a person is formally authorized by the company to do so.

“So in essence you would not be able to use a messenger or courier just to file a document, but you will require an individual specifically authorized and registered for such purpose,” Campos-Vargas says.

“It is absurd to think that you have to authorize an individual to appear before a window to deliver documents.”

Mergers are also come with burdens when dealing with COFEPRIS. Although a merger between two companies implies the complete transfer of rights and obligations, COFEPRIS requires that each specific marketing authorization is amended or transferred prior to the merger.

“This implies that COFEPRIS chooses to ignore the fact that under commercial law the merger implies on its own the complete transfer of rights and obligations, which of course would include marketing authorizations,” Campos-Vargas says. “So you may have a perfect merger, but for practical purposes COFEPRIS will not recognize the merging company as the new holder of the marketing authorization but may, and will, consider that the prior holder is nonexistent and thus proceed with the cancellation of its marketing authorization.”

THE SILVER LINING

Although COFEPRIS is filled with burdensome requirements, Campos-Vargas says that the red tape also acts as an opportunity for drugmakers with its clarity.

“We have a lot of red tape, but we have a clear red tape,” he says. “So in that sense, investing or having a company in the pharmaceutical industry in Mexico is quite straightforward.”

COFEPRIS has additionally become “much more open,” and has made several operational improvements in recent years, Campos-Vargas says.

“We are seeing better timing for sanitary registry and better timing for operation permits,” he says. “From an operational perspective, they have improved a lot.”

The agency has also made some improvements to its drug approval process in recent years. The conventional approval process takes roughly one year, although COFEPRIS has introduced a few regulatory pathways to speed up approvals of certain drugs. For example, companies with a product already approved in certain jurisdictions, such as FDA approval in the US, can gain Mexican approval in a faster manner.

Companies can also hire an “Authorized Third Party,” such as a private laboratory, to help cut down approval time. These Authorized Third Parties – which are approved by the Mexican government – conduct a pre-review of approval documents. If the third party issues a positive report on the product, it can submit the report with the approval documents to COFEPRIS, which subjects the product to a faster review time.

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Adverse Event Assessment In India Gets Harvard-Built Tool; Will Increased Trial Activity Follow?

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The Indian Society for Clinical Research (ISCR) has developed a causality assessment portal in collaboration with Harvard University’s Multi-Regional Clinical Trials (MRCT) Center which it hopes will facilitate a more “reasoned” evaluation of the likelihood of a causal connection between an investigational medicine and an adverse event in trials.

An endorsement of the tool by the country’s regulators (and there are some encouraging early signs) could, alongside other ongoing efforts to streamline the regulatory process, help foster clinical trial activity in India. Trial activity in the country seems to have stagnated in recent years, especially against the backdrop of regulations that directly link trial participant compensation for injury or death to causality assessment—an area where some feel the burden of proof was “in the wrong direction.”

Shoibal Mukherjee, a former chief medical officer at Quintiles India and ex-medical director of Pfizer India, told the Pink Sheet that the Indian regulation requires that causality be assessed for every serious adverse event on a single case basis in order to decide whether compensation is payable or not.

Mukherjee, who is among the experts who played a key role in developing the new causality assessment tool, explained that in the absence of any “easy-to-use algorithm” causality was being assigned subjectively. This lead to a situation where the same adverse event under similar circumstances was deemed study-related for one patient at one location and not study-related for another patient at another location within the same clinical trial.

“The ISCR-MRCT tool helps standardize the assessment process by getting assessors to respond to a comprehensive set of questions, and uses an algorithm to classify causality into four likelihood categories aligned to the WHO-UMC system,” Mukherjee, currently an independent pharma research consultant, said.

The WHO-UMC system is essentially a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Mukherjee expects the ISCR-MRCT initiative to “remove subjectivity” and result in a more reasoned causality assessment.

Adverse event causation is rarely a clear-cut decision, Barbara Bierer, professor of medicine, Harvard Medical School and faculty co-director, MRCT Center, has noted. A frank scientific assessment would often have to use terms like “it’s possible, probable, unlikely or highly likely. And here in India it’s either yes or no, and it’s not a yes or no in medicine. It’s just not the way to think about that,” she said. (Also see “Experts slam crippling Indian trial regulations” - Pink Sheet, 3 Nov, 2014.)

ENHANCED STANDARDIZATION

ISCR, whose members include several large multinational firms and clinical research organizations, feels the new initiative offers a major step forward in standardizing the assessment of causality in clinical trials and suggests that this need not be viewed just in an India-specific context since causality assessment is the same globally.

ISCR president Suneela Thatte told the Pink Sheet that while numerous methods for causality assessment of adverse events have been published in the past, few have focused on the issue exclusively from a clinical trials perspective.

“The WHO-UMC system of standardized case causality assessment provides a structure that can be applied to adverse events in clinical trials, but may lack the degree of standardization as may be necessary in the face of emerging regulatory and ethical requirements as well as to support earlier insights into asset risk profile,” Thatte said.

She hopes that the use of the ISCR-MRCT framework, supported by training initiatives and information technology tools, will enhance standardization of case causality assessment in clinical trials and allow “greater reliance” on the use of the WHO-UMC system in clinical research.

The new portal is expected to serve as a tool that provides guidance documents and training materials to enable clinicians
and ethics committee members to follow best practice procedures in determining causality for adverse events in trials, ISCR said at the time of its 10th annual conference earlier this month.

**REGULATORY BUY-IN**

Asked whether the ISCR-MRCT initiative has the buy-in of the Indian regulator, Thatte said: “We have not as yet demonstrated the tool with the regulatory authorities but plan to do so shortly. The tool was launched at our recently concluded ISCR annual conference and feedback from participants was very positive.”

The regulator’s endorsement for the initiative, though not really mandatory, would clearly be welcome. Thatte indicated that the tool did entail taking inputs from “senior academicians” in India.

Joint Drugs Controller of India VG Somani termed the ISCR-MRCT initiative as a “good” one, especially since not everyone has requisite expertise in the area. The regulator is “supportive” of such efforts, he told the Pink Sheet at the sidelines of the Indian Pharmaceutical Forum 2017 in Mumbai Feb 23.

Mukherjee noted that several workshops were conducted by ISCR over the last two years and the tool has been modified based on feedback from these workshops. But use of the new tool, or any other, is not a regulatory requirement, he emphasized. “However, clinical trial investigators have welcomed the initiative as helpful to grappling with the onerous demands of causality assessment.”

**CHANGES SINCE 2014**

India mandates financial compensation in the case of clinical trial related injury or death; sponsors or their representative are required to pay compensation as per the orders of the Drugs Controller General of India (DCGI). Financial compensation is determined over and above expenses incurred on medical management of the trial subject.

India had previously determined that in case of trial-related serious adverse event (SAE) of death, the DCGI will decide the quantum of compensation, after considering the recommendation of an independent expert committee constituted for that purpose. Among a host of other details on the issue, the government order specifies a formula for determining the quantum of compensation for trial-related death in India. For trial-related SAEs other than death, the regulator’s decision on the compensation will consider the reports of the investigator, sponsor and ethics committee, with an option to constitute an expert panel to advise the DCGI as well.

Asked how the current enforcement regime for trial compensation rules in India have played out since the tweaked rules were announced late 2014, ISCR’s Thatte said that based on feedback received from members so far, the revised compensation guidelines and compensation formula seem to be “working well.”

“Not only is there more predictability and objectivity in the system, but the review process is also very thorough. However, the robustness of the system will be tested when more clinical trials are initiated in the country in the future,” she added.

Some experts, though, referred to the general decline in the volume of trials in India and the resultant “smaller significance” matters such as compensation have taken. “The kind of trials being undertaken in the country now are of the Phase IIIb and Phase IV kind that need to be done to access/support the Indian market, not the cutting edge high-quality global and/or scientific clinical research that India was increasingly participating in prior to 2011,” an expert said. Between 2009 and 2011 were generally the heady years of the Indian clinical research segment, with trial approvals at a peak of 500 in 2010, though the numbers have fallen since.

India’s clinical research sector has, in general, been dented amid uncertainties and delays caused by evolving regulations and ongoing trial-related litigation among other factors. There have, however, been concerted efforts over the recent past to streamline the regulatory process. Last year Informa’s Trialtrove noted how the “rosy view” of India as a location for relatively low-cost clinical trials with a readily available, treatment-naïve patient population became shaded over the past five years by an untenable time to approval.

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The OTC drug industry targets amending the Affordable Care Act to once again allow direct purchases of nonprescription drugs with pre-tax savings accounts, unlike the broad focus by the Republican majority in Congress and President Trump to repeal or replace ACA.

Meanwhile, dietary supplements would be eligible for the first time for purchases using flexible spending, healthy savings and other pre-tax savings accounts under separate legislation proposing changes in health-care spending rules that would be made with repeal of the ACA.


The legislation “would enhance access to care with a benefit for consumers that they lost when the ACA first went into effect. So it’s really about ‘restoring,’ not just ‘repairing’ or ‘repealing,’” said a Consumer Healthcare Products Association spokesman.

Amending the ACA to eliminate the requirement has been CHPA’s top goal since former President Obama’s landmark health care reform law was enacted in 2010.

CHPA, other industry trade and lobby groups and professional associations including the American Medical Association and America’s Health Insurance Plans emphasized the benefits of allowing direct OTC drug purchases with FSA and HSAs in recent letters to the authors of H.R.394 and S.85.

The goal of the ACA “was to expand access to affordable care. Unfortunately, the provision that limits coverage of OTC medicines instead increases overall costs to the health care system and places an administrative burden on already over-burdened physician offices,” the groups, organized as the Health Choices Coalition, said in the letters to Sens. Roberts and Heitkamp and Reps. Jenkins and Kind.

The coalition notes CHPA-commissioned surveys published in 2010 and 2012 that, among other data points, suggested that more than 90% of US consumers prefer using OTCs before seeing a health care provider about a condition or illness, and that nearly 90% of the physicians and pharmacists surveyed recommend consumers self-treat with OTC medicines prior to seeing a doctor. (Also see “CHPA Quantifies OTCs’ Overall Value To Promote Expanded Access” - Pink Sheet, 6 Feb, 2012.)

However, “an overwhelming majority of pharmacists and physicians have … an increased burden on their practices because of” the ACA’s requirement to have prescriptions to buy OTCs using pre-tax savings accounts. – Health Choices Coalition

Introduced since the ACA was passed, but the legislation has progressed only as far as passing the House in 2016 while gaining no traction in the Senate. (Also see “OTC Drug Industry Could Stand To Gain With ‘Pragmatist’ In White House” - Pink Sheet, 11 Nov, 2016.)

**ACA REPEAL CHANNELS TAX REFORM**

The Health Savings Act of 2017, S.403 and H.R. 1175, introduced by Sen. Orrin Hatch, R-UT, and Rep. Erik Paulsen, R-MN, proposes allowing dietary supplements to be considered deductible medical expenses under FSA, HSA and similar accounts among a broad swath of changes it proposes to replace the ACA.

Other health-care spending topics covered in the bill include renaming high-deductible health insurance plans as HSA-qualified health plans; expanding access to pre-tax savings accounts to consumers receiving public medical or health care assistance; simplifying administrative issues related to maintaining pre-tax health savings accounts; eliminating the Rx requirement for purchasing OTCs with the accounts; and also adding exercise programs and preventive screening tests as deductible charges those accounts.

Bills to make supplements eligible for pre-tax account spending were filed for the first time in 2016 by industry champion Hatch
First Generic Approvals Decline For Fourth Straight Year At US FDA

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First time generic approvals at the US FDA have declined for a fourth straight year, although the drop could simply be a product of timing and workflow.

In the waning months of the first iteration of the Generic Drugs User Fee Act, FDA announced that it approved 73 first time generics – an alternative for a brand name product where there was previously none – in 2016, a nearly 20% dip from the 90 approved in 2015. The Office of Generic Drugs' (OGD) 2016 annual report largely highlighted its record-setting approval numbers: the agency approved 630 abbreviated new drug applications (ANDAs) and tentatively approved 183 last year, the highest totals in the history of the generic drug program.

"FDA considers first generics to be important to public health and prioritizes review of these submissions," an agency spokesman tells the Pink Sheet. "The agency approved 630 abbreviated new drug applications (ANDAs) and tentatively approved 183 last year, the highest totals in the history of the generic drug program."

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First generic approvals increased sharply from 94 to 152 from 2011 to 2012. Since then, they dropped to 106 in 2013, 97 in 2014, 90 in 2015 and 73 in 2016.

The report also noted several notable first generics the agency approved in 2016, including for Daiichi Sankyo Co. Ltd.’s Benicar (olmesartan), Pfizer Inc.’s Viagra (sildenafil), AstraZeneca PLC’s Crestor (rosuvastatin) and Genentech Inc.’s Tamiflu (oseltamivir).

CLEARING THE BACKLOG
FDA noted in the report that it had met its GDUFA commitment more than a year in advance to take a first action on 90% of the ANDAs and prior approval supplements (PAS) in process with FDA or industry prior to Oct. 1, 2012. According to the report, the agency completed first actions on 95% of the 2,866 ANDAs and 93% of the 1,873 PAs as of Dec. 31, 2016.

Many of these first actions, however,
have consisted of complete response letters. Of the 2,729 ANDAs in the backlog for which the agency has performed a first action, 1,554 have received complete response letters. Only 676 have been approved and 166 have received tentative approval. For the 1,745 PASs in the backlog, 998 have been approved, four have been tentatively approved and 480 resulted in a complete response letter.

At the end of 2015, OGD completed first actions on 84% of the ANDAs and 88% of the PASs in its backlog. (Also see “ANDA Backlog: FDA Climbs The Mountain, Will Need To Climb It Again” - Pink Sheet, 13 Apr, 2016.)

The 630 ANDA approvals and 183 tentative approvals in 2016 surpass both respective totals from 2015 of 580 and 146.

OGD also published more than 200 product-specific guidances related to developing generic drugs, bringing the total posted on FDA’s website to more than 1,500, and revised 91 product-specific guidances.

Additionally, the agency awarded funding to 16 new external researchers “to conduct regulatory science that will complement internal activities,” bringing OGD’s total of ongoing external research collaborations to 87 at the end of 2016.

UPCOMING HEARING

The report was released on the shortly ahead of an upcoming House Energy and Commerce Subcommittee on Health March 2 hearing titled “Examining FDA’s Generic Drug and Biosimilar User Fee Programs.” Witnesses have not yet been announced, but the committee’s notice on the hearing reads that “FDA and other relevant stakeholders will provide testimony on how the programs have been implemented to date and present recommendations pertaining to their reauthorization.”

The Subcommittee on Health will additionally consider the Lower Drug Costs Through Competition Act (H.R. 749), sponsored by Rep. Kurt Schrader, D-Ore., and Gus Bilirakis, R-Fla. The legislation would direct FDA to conduct faster reviews for generics that would alleviate at shortage or be the first competitor in a market. Once the drug “has a sustained market presence” the sponsor would also receive a “transferable generic drug priority review voucher.” (Also see “Drug Pricing Bill May Make Six-Month ANDA Review Slower Than Eight-Month Review” - Pink Sheet, 2 Feb, 2017.)

The generics industry has not embraced the bill, with many believing it does not address the fundamental challenges that products often face in coming to market and staying there.

FDA doesn’t appear as though it would be enthusiastic about the legislation either. OGD has previously noted that it already aims to prioritize the approvals of first generics. (Also see “GDUFA II: Priority Reviews Considered For Some ANDAs” - Pink Sheet, 6 Nov, 2015.) The agency also wouldn’t likely take too kindly to another priority review voucher program, as it has already expressed its displeasure with the burden imposed by the rare pediatric disease priority review voucher program. (Also see “Review Voucher Program For Rare Pediatric Diseases Should Not Be Reauthorized, US FDA Says” - Pink Sheet, 3 Mar, 2016.)

The 630 ANDA approvals and 183 tentative approvals in 2016 surpass both respective totals from 2015. First generic approvals increased sharply from 94 to 152 from 2011 to 2012. Since then, they have dropped.
FDA Urges Full Participation In Quality Metrics Program

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Pharmaceutical companies should participate in FDA’s quality metrics program and submit metrics data once an electronic portal goes live Jan. 1, 2018, Ashley Boam, acting director for the FDA’s Office of Policy for Pharmaceutical Quality, said Feb. 22 at the Parenteral Drug Association’s meeting on quality metrics and quality culture in Bethesda Md.

Without participation, the program will not succeed, as FDA will not have enough information to predict drug shortages and the industry will not see regulatory relief, Boam said.

In November, FDA issued revised draft guidance on a pilot program to collect quality metrics data from pharmaceutical manufacturers. The revised draft was stripped of a mandatory reporting requirement, quality culture metrics and an on-time product review metric. FDA is no longer insisting on product metrics, allowing a site metric alternative. (Also see “FDA’s Revised Quality Metrics Program: Voluntary Now, Mandatory Later” – Pink Sheet, 27 Nov, 2016.)

The three metrics the agency is starting with are lot acceptance rate, product quality complaint rate and invalidated out-of-specification rate. FDA is planning to open an electronic portal in January 2018 for voluntary submission of quarterly metrics data.

Boam said that a current priority for the agency is to focus on testing the portal that will collect the electronic metrics data. “Our intent is once we start collecting this information we will then publish a report to give the industry some kind of indication of what information the agency is receiving.”

Boam said that FDA is also welcoming ideas on how to develop a reporter’s list to encourage quality metrics reporting. FDA’s guidance said that to help spur participation, the agency intends to publish a list of the names of establishments that report quality data. FDA said that the list may be useful to manufacturers when selecting contract manufacturers and component suppliers that are also on the list.

She discussed some of the benefits of participating in the metrics program for both FDA and industry. For FDA, the metrics program allows the agency to better focus its resources on the areas of highest risk to public health. “If we have metrics we can get an idea of what is working well and it allows us to be more efficient in our inspections, that means that we can get in and get out. That frees up your resources and ours.”

For industry, participation offers the promise of potentially getting inspected with less frequency and being subject to less stringent change control requirements.

Boam said that for FDA, a benefit of the metrics program is being able to perform predictive analytics from the metrics data and to link this to inspection outcomes, recalls and field alert reports, and to be able to predict drug supply disruption and potential drug shortages.

Yet she said this program can only be successful if the entire industry participates, because a large body of data is needed to draw the most meaningful conclusions about the site or product.

“This has been one of the challenges for us in moving from a mandatory to a voluntary program, is getting good data and getting folks to participate. … This will be dependent on us getting good data across the spectrum. If only the A-plus children turn in their test papers and everybody looks great, we will not learn whether the analytics in the program will predict problematic situations that come up. We are trying to incentivize manufacturers, small, large, experienced, not experienced. We really want data from folks in all of those different scenarios because it gives us the ability to see differences. If we only get data from the A-plus students, we will not be able to do that.”

Boam said that while the metrics program is currently voluntary, Section 706 of the FDA Safety and Innovation Act gives the agency the authority to request records for a future mandatory program. Section 706 allows the agency to collect records normally available for inspection in advance of or in lieu of an inspection. Yet the pharmaceutical industry disagrees with the agency on this issue and said that FDA cannot force drug makers to collect and report quality metrics without first going through a rulemaking process. (Also see “FDA Quality Metrics Proposal Sparks Objections, Disarray” – Pink Sheet, 25 Sep, 2015.)

Boam said that FDA is continuing to plan for notice and comment rulemaking.

From the editors of Gold Sheet. Published online February 24, 2017
The warning letter, addressed to Pfizer CEO Ian Reed, said the violations are similar to those cited in four other warning letters FDA sent Hospira over the past six years.

CARDBOARD FOUND BUT NOT ELIMINATED

During the inspection, which ran from May 16 to June 8, 2016, FDA investigators reviewed reports from multiple particulate-related complaint investigations that identified the problems but failed to ascertain their full extent or to resolve them. In one case, Hospira determined in response to a December 2015 complaint about particulates in a vial of vancomycin hydrochloride that the source was cardboard, and it was probably related to handling of vial stoppers. However, Hospira closed the investigation after just six weeks without evaluating the full extent of contamination or taking further corrective actions. The company didn’t even take further action after receiving additional complaints of particulates that turned out to be cardboard in other vials of the same lot, FDA said. Hospira finally recalled the lot in May 2016, more than four months after the first report of contamination and just 10 days before FDA launched its three-week plant inspection.

MYSTERY PARTICULATES RETAINED

In another case, Hospira examined samples of particulate-tainted vials of 30 mg/ml ketorolac tromethamine injection that a customer returned and confirmed that they contained particulates, as did 190 retention samples from the same lot. Hospira’s subsequent investigation

facturers of just how important it is to FDA that they control visible particulates. It’s worth noting, however, that August 2014 guidance from the US Pharmacopeia on visual inspection of parenterals appears to have reduced the frequency of FDA inspectional observations in this area. (Also see “FDA Investigators Finding Fewer Deficiencies For Visual Inspection Programs” - Pink Sheet, 28 Sep, 2016.)
focused on brown agglomerates that appeared during production of the lot in question. The investigation relied on analysis of just 10 retention samples and failed to ascertain the contaminant’s identity and source, FDA complained.

In the end, Hospira released the lot because the contaminant “was intrinsic to the manufacturing process” but failed to check whether other lots were affected, or to document any corrective actions.

**DEFECT LIMITS PURPOSEFULLY IGNORED**

FDA criticized Hospira’s visual inspection procedures for instructing operators to ignore established in-process defect limits whenever the company changed its manufacturing process.

The warning letter suggested that “the lack of defect limits for visual inspections may have resulted in the release of products that otherwise would not have been distributed.”

FDA also raised concerns in the warning letter regarding poor aseptic and personnel monitoring techniques.

There was also a problem with the procedure for operating the plant’s online semi-automated visual inspection of vials: operators were not required to quarantine initially rejected units for later re-inspection. This meant potentially defective units could wind up back in the manufacturing process.

FDA also found evidence of inadequate sampling plans and post-market reporting violations.

**PREVIOUS VISIBLE PARTICULATE ISSUES**

FDA mentioned visible particulates in two of the four previous Hospira warning letters that the agency said raised similar issues.

An April 2010 multi-site warning letter noted that problems with stainless steel particulates in sterile injectable emulsions at the plant Hospira operated at the time in Clayton, NC, had persisted at least since 2007.

A September 2014 warning letter concerning a Hospira plant in Mulgrave, Australia, said that in September 2012, a customer alerted the company to visible particulates in a sterile injectable product, but that the company did not alert physicians to visually inspect the vials and use filters until March 2014.

**A BIG EMPHASIS ON COMPLAINT HANDLING**

The latest warning letter comes five years after Hospira responded to the April 2010 warning letter and an ensuing drug shortage crisis by upgrading the company’s field alert reporting and complaint-handling processes. (Also see “FDA Calls for Greater Compliance With FAR Reporting Requirements” - Pink Sheet, 28 Mar, 2013.)

FDA’s most recent inspection findings suggest that, at least for the McPherson plant, there is more work to be done to align the company’s complaint investigations with FDA’s expectations.

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## Recent And Upcoming FDA Advisory Committee Meetings

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<td>Strain selection recommendations for influenza virus vaccines for the 2017-2018 flu season</td>
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<td>Premarketing and postmarketing data about the abuse of Endo’s Opana ER (oxymorphone extended-release), and abuse of generic extended-release and immediate-release oxymorphone products</td>
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