BIOSIMILARS
Biological Product Suffix Submissions Limited To 10 Candidates By US FDA, p. 15

MANUFACTURING QUALITY
US FDA's Foreign Inspection Agenda: Visit The 1,000 Facilities It's Never Seen, p. 19

REGULATORY UPDATE
Industry Communications With Payors: US FDA Okays Info On Investigational Drugs, p. 11

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NHS Changes Would Jeopardize Life Science Sector – BIA; 'Hard' Brexit Looms

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Proposals by health technology assessment body NICE and NHS England to change their processes in order to deal with medicines with a high budget impact will hinder access to highly innovative and first-to-market drugs, according to the UK Biotechnology Industry Association.

The proposals will also jeopardize the future of the UK's "world-leading life science sector" amid the uncertainty that is already being caused by Brexit, the trade group said in comments published shortly before prime minister Theresa May announced on Jan. 17 that the UK will not be remaining within the EU single market.

The changes being proposed by NICE and NHS England include a maximum cost-effectiveness level for ultra-orphan drugs and a "budget impact threshold" that would trigger the need for special arrangements on particular drugs. They run counter to initiatives such as the government's focus on industrial strategy, the Biomedical Catalyst, the need to positively showcase the UK during Brexit and the recommendations of the Accelerated Access Review, according to the BIA.

The NHS must be better able to support and use innovation to the benefit of both UK health and the broader innovation agenda, the association said, but by making it more difficult for patients to access highly innovative drugs, the changes proposed in the consultation "undermine this agenda and put the future of the UK's world-leading life sciences sectors at risk."

As the UK prepares to leave the EU, "the delivery of an internationally-competitive industrial environment for the bioscience and life-sciences sector is more important than ever," the BIA declared.

Its concerns will not have been alleviated by May's declaration that the UK "cannot possibly" remain within the EU single market, although at least the government's Brexit cards are now more or less on the table.

While not unexpected, the announcement has confirmed fears among many in the biopharmaceutical industry that the government is planning for a "hard Brexit" that will have wide-ranging implications for the way that the UK life sciences sector operates within the EU, particularly given its involvement in the EU legislative and regulatory framework, its participation in European research projects, and its reliance on the mobility of staff from country to country.

Whether industry is impressed by the prime minister's pledge to seek a "bold and ambitious free trade agreement" with the EU and the "greatest possible access to the single market" remains to be seen.

After the announcement, BIA CEO Steve Bates said it was good that May had recognized the need to "continue to collaborate

CONTINUED ON PAGE 4

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5


7


14

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Trump Takes Office, Change At US FDA Arrives With 'Beachhead Teams'

http://bit.ly/2kaNMXQ

Incoming president not holding over any FDA political appointees from the Obama administration, but what exactly his stamp on the agency will be remains unclear.

7 Biosimilars, 2 ATMPs Among 81 Medicines That Got EMA Nod in 2016

http://bit.ly/2k4ooyU

In 2016, oncology drugs again topped the list of medicines for which the European Medicines Agency recommended a centralized marketing authorization.

Make Interchangeability Great Again: Biosimilar Switching Studies Need US Comparators

http://bit.ly/2jV2fnk

Sandoz, which used an EU-approved comparator in the switch study for its biosimilar Erelzi, might have to redo the trial in light of FDA's draft guidance.

HHS Nominee Price Sidesteps Medicare Drug Pricing Negotiation Questions

http://bit.ly/2jxpkNf

Confirmation hearing for Rep. Tom Price centers on Obamacare repeal, but also addresses whether he would be aligned with President-elect Donald Trump in supporting government negotiation on drug prices.

Drug Pricing: PhRMA Report Aims To Shift Focus To Supply Chain

http://bit.ly/2jHTAYt

More than one-third of gross sales for brands is eaten up by rebates, discounts and fees, a study finds, raising questions about whether price concessions provided to payers are 'flowing to patients,' PhRMA President Stephen Ubl says.

inside:

CONTINUED FROM COVER

with our European partners on major science, research, and technology initiatives," but he repeated industry's warnings about the need for some form of regulatory co-operation agreement for life sciences.

He said medicines regulation was an area where the UK and the remaining member states had "adhered to the same rules for over 40 years." It fitted the prime minister's criteria for being an area where it 'makes no sense to start again from scratch' and it could be a 'specific European programme' in which the UK 'might want to participate'," said Bates, referring to portions of May's speech.

"Drugs are the part of NHS care most integrated with the European Union and therefore drug regulation will need the closest attention to avoid a disruptive cliff edge for patients in both the UK and EU. Here I believe the process of, and industry expertise made available to, the UK government through the work of the UK EU Life Science Steering Committee should be useful," he declared

> "Drug regulation will need the closest attention to avoid a disruptive cliff edge for patients" – BIA CEO Steve Bates

THE NICE/NHS PLANS

The NICE/NHS England proposals, which were announced in October last year, include a new fast-track option for appraising technologies that offer "exceptional value for money" – i.e., those with a quality adjusted life year (QALY) of up to £10,000 ($12,400).

They also suggest a maximum cost-effectiveness level of £100,000 per QALY for products for very rare diseases assessed under the NICE's highly specialized technologies (HST) program that would mean products with a QALY over this level would not automatically qualify for funding on the NHS.

On top of that, a "budget impact threshold" of £20m a year could be introduced to "signal the need to develop special arrangements for the sustainable introduction of cost effective new technologies." ([A#PS119576]) The idea appears to be one approach to dealing with the arrival of very high-cost therapies such as the newer hepatitis C drugs.

Launching a consultation on the plans in October, Sir Andrew Dillon, NICE chief executive, said the proposals represented "a fair approach to the significant challenge of providing faster access to innovative, cost effective treatments alongside the need to safeguard future financial sustainability."

But the BIA has launched a scathing attack on the proposed changes, saying that a maximum QALY for HST drugs would "effectively stop the flow of new medicines reaching patients with very rare and complex diseases," while a budget impact threshold meant evaluations and funding decisions would become more "arbitrary" and inconsistent.

The BIA has outlined its concerns in its formal response to the consultation, which ended on Jan. 13. It rejects outright the notion of a cost per QALY above which funding is not automatically provided for HST drugs, which are usually "ultra-orphan" products. Such thresholds, it says, are not appropriate for evaluating ultra-orphan medicines because of the small patient populations, often limited data and "uncertainty in the figures produced."

This was recognized by NICE when it established the HST program, which provides a "distinct pathway for the appraisal of medicines for very rare diseases," the BIA says. "The consultation provides no evidence or rationale to explain why NHS England and NICE now wish to change their position on using QALYs to assess HSTs."

NICE and NHS England point out that a £100,000 QALY threshold for HST evaluations would be five times higher than the lower end of NICE's standard threshold (£20,000 per QALY). However, the BIA says that none of the drugs approved under the HST process so far have had a QALY below £100,000. Those that have received a positive recommendation – PTC Therapeutics Inc.'s PTC Therapeutics Inc.'s *Translarna*, Alexion Pharmaceuticals Inc.'s *Soliris* and BioMarin Pharmaceutical Inc.'s *Vimizim* – had incremental cost ratios of between £521,000 and £830,000 per QALY, it points out.

Under the proposals, any HST-evaluated products that exceeded the £100,000 level would be considered through NHS England's specialized commissioning prioritization process. Again the BIA is critical, describing the prioritization process as "not fit for purpose."

The current NICE HST program, while not perfect, provides a "transparent and robust process, one through which industry and patient groups can engage, with limited emphasis on QALY thresholds and a more holistic assessment of value," the BIA says.

In contrast, the NHS prioritization process uses "a crude 'cost per patient' methodology which fails to take into account unmet medical need, burden of illness and impact on patients and carers." NHS England would need to make significant changes to the process, such as including a premium for rarity, in order to render it suitable for purpose for evaluating ultra-orphan medicines, it adds.

The industry body is similarly dismissive of the proposed £20m "budget impact threshold", saying it would represent "a fundamental shift" in the way medicines are appraised and patients gain access to innovative therapies in England.

"If a budget impact threshold is introduced there is a concern that evaluations and funding decisions will become more arbitrary – perhaps based on prevailing political and economic concerns– and lack consistency or predictability. Moreover, the introduction of a budget impact threshold would disproportionately affect highly innovative and first to market products."

The BIA also notes that its member companies have told it that accurately estimating budget impact can be "incredibly complex and difficult given uncertainty regarding the number of patients who may come forward for treatment and the competitive marketing landscape."

The possible drawbacks of a budget impact threshold were also outlined by lawyer Sam Samaratunga of Keystone Law, who said that if the impact of a new technology was thought likely to exceed £20m a year, NICE could pause the appraisal process and ask the company to engage with NHS England in order to discuss and agree commercial terms before proceeding with the appraisal process. "This may impact the likelihood of companies willing to take up opportunities to develop treatments for rare diseases," Samaratunga said.

FAST-TRACK PROCESS

While industry might be expected to welcome the proposed fast-track process proposed by NICE and NHS England, the BIA has afforded it only a lukewarm reception, saying that such a process should not be defined by an economic threshold that applies to "a very small number of products."

Highly innovative, first-to-market medicines are "extremely unlikely" to achieve a cost-effectiveness ratio of £10,000 per QALY, the association said. Any additional fast-track process should be aligned with existing programs that prioritize "highly innovative, transformative medicines", such as the Early Access to Medicines Scheme (EAMS), rather than "diverting resources away from them."

Something else that is not clear is how these proposals will sit alongside the recommendations made last year in the Accelerated Access Review, which are intended to help identify and accelerate take-up of those innovations that are seen as most significant in terms of benefits to patients while keeping NHS costs affordable.

The review, which included recommendations such as a new "transformative designation" for strategically important products and a stakeholder partnership to prioritize their entry into an accelerated access pathway, was warmly welcomed by the biopharmaceutical industry, although it stressed the importance of taking the recommendations forward, particularly in the context of Brexit.

According to the BIA, these latest proposals, particularly the fast-track process, could take the focus away from the need to address barriers that lead to delays in existing evaluation processes, and might conflict with the ideas and recommendations in the AAR.

The AAR's final report, it notes, includes recommendations to make it easier for patients to access innovative medicines and other products. "NHS England and NICE should ensure that the changes proposed in the consultation align with, rather than undermine, the AAR's whole-system approach."

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UK Industry Pleased With Brexit Committee's Focus On Regulation

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The UK Parliament's "Brexit Committee" has published its first report on how the government should proceed in its negotiations over leaving the EU. While the report does not go into any real detail as far as the life sciences are concerned, the UK pharmaceutical industry has welcomed what it calls the committee's "focus on the importance of getting medicine regulation right" on day one of Brexit.

The Exiting the EU Committee includes members of Parliament from across the parliamentary spectrum. Its report, published Jan. 14, calls on the government to publish its "Brexit plan," including its position on membership of the EU single market and the customs union, by mid-February at the latest. It said ministers should seek an outline framework on the UK's future trading relationship with the EU as part of the Article 50 negotiations, including "appropriate transitional arrangements."

In one of the few specific mentions of the life sciences sector, the report says there are a number of areas where legal certainty would be needed on the day of exit, including the transfer of regulatory and policing responsibilities in areas such as pharmaceuticals, genetically modified food and competition law, as well as the way in which sensitive information is handled.

It also says that the UK's future relationship with the European Medi-

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> The report says there are a number of areas where legal certainty would be needed on the day of exit, including the transfer of regulatory and policing responsibilities in areas such as pharmaceuticals, as well as the way in which sensitive information is handled.

cines Agency and other EU agencies would be defined in the Brexit negotiations. "The extent to which the UK wishes to continue to co-operate with these bodies or continue membership, duplicate their functions in the UK or dispense entirely or partially with the function that they perform will be matters for domestic political decision and negotiation with counterparties representing the EU," it declares.

It continues: "It will be essential to provide clarity as soon as possible, and certainly by the time the UK leaves the EU, about the government's preferred option for the UK's future participation in EU regulatory bodies. If it is decided, however, not to seek to maintain membership of these bodies then the government must set out the new arrangements it proposes to put in place to ensure that these functions are carried out in future."

Mike Thompson, chief executive of the Association of the British Pharmaceutical Industry, said: "Securing continued regulatory cooperation and alignment with the EU for medicines will be in the best interest of the UK government, EU member states and patients."

Thompson said APBI was "confident that government understands that any transitional arrangements should not put patient access to medicines under threat" and that the industry would continue to work with the government "to make sure this happens as smoothly as possible."

The biopharmaceutical industry has already made clear that its priorities for a post-Brexit UK include continued regulatory alignment, access to the best talent, movement of products, and predictable funding and collaboration in scientific research.

REGULATORY CLARITY NEEDED

These and other points were covered by the APBI's executive director of research, medical and innovation, Virginia Acha, when she gave evidence to the committee at its meeting last month in preparation for its report. Acha stressed the importance of ensuring that in the pharmaceuticals area the regulatory situation was clear on the day the UK left the EU.

UK biopharma's post-Brexit priorities include continued regulatory alignment, access to the best talent, movement of products, and predictable funding and collaboration in scientific research.

"I have to make sure that medicines from day one have all the right regulatory approvals, labels and patient information leaflets. It is all bound up in law – patients depend on us to have it right on day one," Acha said. Industry was looking at how to prioritize this work and do it as simply as possible, she noted: "We're starting to give people an understanding of what to do as a company to prepare for day one, this is what people are expecting."

As for the effects on regulatory harmonization, Acha said that EMA, in tandem with the International Council on Harmonization and the World Health Organization, had been a "critical voice" in using science to converge to the best possible regulatory standards, as had the UK regulator, the Medicines and Healthcare products Regulatory Agency.

"The regulations we have today are where we have global agreement, so for a global industry like mine that is important to keep to," she said. "We would like to be able to continue wherever possible to be able to continue within that global regulatory agreed process" in a "bespoke way, and we are very hopeful this is something that can be agreed."

Specifically on the new EU Clinical Trials Regulation, which is set to bring simpler, more harmonized rules on running clinical trials, including a single portal for trial applications, from October 2018, Acha said: "If we can continue to work in the cooperation we have established under the EMA network, this just makes it quicker and easier, and in fact the use of the portal would be useful, especially since we have invested quite a lot of time and energy in putting it together, but all of these things may not be within our gift."

Regarding the impact of the EMA relocating to another member state, and whether companies might follow it, Acha said the agency was indeed one reason for companies to invest in "bricks and mortar" in the UK, but that there were "plenty of other reasons to be here." She said in her view companies would "never make an investment decision based on where the regulator is."

The EMA had "of course made huge contributions," and that was the reason why "you have seven or eight countries now bidding for it." However, she said, that was not the only reason why a company would be based in the UK, and it was not the only reason why a company would leave.

From the editors of Scrip Regulatory Affairs.
Published online January 13, 2017

FROM OUR DIGITAL ARCHIVES

To gain further perspectives on Brexit:

- *"Post-Brexit UK Could Be 'Back Of The Queue' For Drug Access, Warns MHRA Chair" – Pink Sheet, Jan. 10, 2017.*
- *"Brexit: EMA Could Lose Up To Half Its Staff If It Has To Move" – Pink Sheet, Dec. 2, 2016.*
- *"Brexit: EMA Has A Visit A Week From Potential Hosts" – Pink Sheet, Dec.2, 2016.*
- *"UK Industry Welcomes R&D Measures In Chancellor's Autumn Statement" – Pink Sheet, Nov. 24, 2016.*
- *"UK Regulator Has Key Role in One in Four EU-Wide Approvals" – Pink Sheet, Nov. 22, 2016.*
- *"New EU Patent System: Only Two More Ratifications Needed, But Will The UK Sign Up?" – Pink Sheet, Sep. 22, 2016.*

Find these online at **pink.pharmamedtechbi.com**.

EMA And National Agency Heads Join Forces On Medicines Availability and Big Data

MAUREEN KENNY maureen.kenny@informa.com

The European Medicines Agency and national agency heads are working together on the availability of medicines and big data in medicines evaluation, the EMA is extending a multinational approach to drug assessment that is reducing the agency's reliance on UK experts in preparation for Brexit, and new guidance is planned by the EMA on data integrity. These are just some of the many regulatory developments that EMA deputy executive director Noel Wathion covered in his presentation at the Annual European Medicines Agency Review of the Year and Outlook for 2017 conference, which took place recently in London.

The Pink Sheet will report in more detail on some of these topics over the coming weeks. In the meantime, here are some basic pointers.

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> A joint working party will look into big data in medicines development and regulatory science. An EMA workshop on the topic was held in November.

AVAILABILITY OF MEDICINES

The availability of medicines is an issue that is very high not only on the political agenda but also in terms of day-to-day operations, Wathion noted. It was also "one of the highest priorities" for both the HMA and the EMA in their work plans for the coming years. A reflection paper on the topic has been developed and was discussed at the meeting of the EU Heads of Medicines Agencies network that took place in the Slovakian capital, Bratislava, at the end of November, Wathion said.

Kristin Raudsepp, the head of Ravimiamet, the Estonian State Agency of Medicines, is the co-chair of a new joint EMA/HMA working group on the subject, representing the national medicines agencies. At the time of the conference, which took place at the beginning of December, the co-chair representing the EMA had yet to be named. The EMA has since told the Pink Sheet that Wathion himself will be the EMA co-chair*.

The EMA and the HMA have agreed to establish a new joint working party that will look into issues relating to big data in medicines development and regulatory science. The decision was taken following what Wathion described as the "successful" workshop the EMA held on this topic last November.

EU NETWORK TRAINING CENTRE & MNATS – PREPARING FOR BREXIT

Wathion went on to discuss two initiatives that, while not new, are being developed as tools that will help the EMA and the broader European medicines regulatory network cope with at least some of the potential consequences of the UK's departure from the EU or Brexit, such as the likely loss of UK expertise.

The initiatives are the EU Network Training Centre (NTC), a project that was agreed to in early 2014 and that exists to strengthen scientific and regulatory capacity across the network, and the multinational assessment team (MNAT) concept** that was launched in late 2012 with a view to increasing the number of national competent authorities (NCAs) involved in the pre-approval assessment of new medicines.

Wathion described the EU NTC as "one of the success stories of the past years" in terms of the EMA and the NCAs working together. It would be, he said, "an important instrument in building up capacity and capability across the network" in the coming years. Nine new curricula for training – still focusing on regulatory authorities – are in the process of being developed and while developing additional new curricula is also being considered, these would have to take into account "any particular needs stemming from a

possible Brexit in terms of the loss of UK expertise."

According to Wathion, there is a lot of sympathy for this initiative, certainly from smaller member states, who see it as an excellent way of "upgrading" their staff, enabling them to take on board more work in terms of the system – regardless of the whether that work relates to centralized, mutual recognition, decentralized or national procedures.

EMA executive director Guido Rasi said recently that the aim was "to try to train experts as fast as we can all over Europe."

With regard to the MNAT concept, Wathion explained that the EMA was expanding the approach to the post-authorization space.

Drug assessments have traditionally been done by a team of experts from one member state. For several years now, though, multinational assessment teams formed according to expertise rather than by country have been able to take part in the assessment of new drugs submitted to the agency under the centralized procedure. For products where an MNAT was used in the pre-authorization phase, MNATs will be able in future to evaluate applications for extensions of indications and line extensions, Wathion said.

The EMA management board subsequently officially agreed to the expansion, starting April 2017, at its meeting in mid-December.

The MNAT approach was another success story, said Wathion, with all but five member states having been involved to some extent.

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Visit **pink.pharmamedtechbi.com/regional-coverage** for articles that provide additional perspective from the event.

THE GLOBAL REGULATORY ENVIRONMENT

Moving on to the global regulatory environment, Wathion mentioned several initiatives that the EMA will start in 2017. Among others things, the agency is planning to develop guidance on data integrity and a procedure for the co-ordination of inspections in third countries.

The London conference was organized jointly by the EMA and TOPRA, The Organisation for Professionals in Regulatory Affairs. The following articles provide additional perspective from the event.

From the editors of Scrip Regulatory Affairs. Published online January 16, 2017

Trump, Congress And The Search For Common Ground On Drug Pricing

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President-elect Donald Trump's drug pricing interventions don't seem likely to find much support among Congressional leaders. But they will drive discussions about what solutions Republicans can be comfortable with.

Trump has kept the issue of drug price controls in the public spotlight by continued criticism of industry practices and vows to address it through government price negotiation. ([A#PS119812])

He repeated his intention to induce drug companies to negotiate prices with the government – and pledged to implement the process for Medicare and Medicaid – in an interview published Jan. 15 in The Washington Post. The industry has been "politically protected, but not anymore," he told the paper.

Earlier on the campaign trail, Trump also threatened to allow US patients access to less expensive drugs imported from abroad. That policy and government pricing negotiation have been debated in Congress for years and staunchly opposed by Republicans, though many Democrats have supported the ideas.

That puts Trump in the position of promoting legislation that is at odds with the ideas of his own party.

Sen. Orrin Hatch, R-UT, who chairs the Finance Committee (which oversees Medicare), recently challenged the prospect of government negotiation in Medicare during hearings with Obama Administration health officials. He expressed concern that the Administration would find a way to authorize HHS price negotiations in the Medicare Part D program without congressional endorsement, maintaining the move would undermine the program and hamper innovation.

And Trump's selection for HHS secretary, Rep. Tom Price, R-Ga., has also opposed HHS negotiations in Part D. The apparent disconnect between that position and Trump's statements may lead some members of the Senate Health, Education, Labor and Pensions Committee to seek clarification of the Administration's intentions during Price's first confirmation hearing Jan. 18.

But it's likely Trump will want to foster an environment of continued uncertainty as a way to push industry to develop voluntary concessions on pricing practices.

As a result, despite longstanding opposition among Republicans, "you still have to keep Medicare negotiation and importation in your realm," of possibilities, Avalere Health Senior VP-Policy Elizabeth Carpenter advised during a Jan. 12 webinar.

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"Given the environment and the change in politics, these are topics that could garner additional debate and potentially new takes as we enter into this new era."

Drug pricing is recognized as a problem on both sides of the aisle, a Senate Republican staffer noted during a recent briefing with reporters. But there are many different ways to exert downward pressure on drug pricing, some more "drastic" than others, he observed.

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Tom Price's confirmation hearings for HHS secretary may be an early barometer of Republican concern, and Democratic appetite, for Trump's pricing agenda.

There is no single "silver bullet" that will solve the pricing problem and maintain the level of innovation that is "critical for the future of the health care sector," the Senate aide observed. He maintained that any action contemplated should be balanced with the need to sustain industry innovation.

Rep. Michael Burgess, R-Texas, has taken a similar position in debates over drug pricing. He has publicly urged the biopharmaceutical industry to take the initiative to figure out a novel payment system for expensive, highly effective new treatments because "you may not like" what the government decides to do. ([A#PS056271]) Burgess is the new chairman of the Energy & Commerce Health Subcommittee.

CONSENSUS AROUND INCREASING COMPETITION

One approach that is likely to find consensus in Congress and the Administration is reducing the backlog of generic drug applications at FDA to allow for more competition in the market, which could be addressed in upcoming user fee reauthorization legislation.

"We continue to believe that the incoming Administration and

Congress will look for ways to increase competition in the market and that could mean changes to things at FDA that encourage quicker product approval or introduce additional competitors," Avalere's Carpenter said. "That could manifest itself as part of the [Prescription Drug User Fee Act] PDUFA debate this fall."

Pharmaceutical Care Management Association President Mark Merritt also believes the idea of lowering prices by promoting competition could find traction in Congress. PCMA is the trade association representing pharmacy benefit managers.

"One thing [I've found] in my discussions on the Hill, in both committee hearings and one-on-one meetings, is there's a real bipartisan appetite for FDA reform, for getting competing drugs to market faster. … I think there'll be a serious look at what we can do to get more competition, drugs approved faster, because that is the key to driving down prices," Merritt said.

Some ways of increasing generic competition would be more problematic for branded drug manufacturers than others. For example, Sen. Chuck Grassley, R-Iowa, advocates restricting patent settlement agreements between manufacturers that delay the introduction of generics.

"He supports measures to bring lower cost drugs to consumers by encouraging competition in the marketplace" and "will continue to do this by overseeing federal agencies to ensure they enforce the law and by introducing legislation when needed," a Grassley spokesperson said in an email.

Grassley and Sen. Amy Klobuchar, D-Minn., re-introduced a "pay-for-delay" reform bill on Jan. 12. "This bill would prevent drug companies from engaging in these abusive dealings and ensures more timely access to affordable medicines for patients and taxpayers," Grassley said in a statement.

Klobuchar and Grassley introduced similar legislation in the last Congress following a Federal Trade Commission report demonstrating a significant number of potential pay-for-delay settlements continues to occur.

Published online January 18, 2017

The Bully Pulpit: Trump Versus Drug Prices

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The immediate reaction in industry to the election day sweep by Republicans (beyond surprise at the unexpected victory of Donald Trump) was a sense of relief: the potential for an all-out battle over drug pricing policy seemingly fell by the wayside.

Trump's comments on drug pricing during the transition – first in a Time "Man of the Year" interview published shortly after the Election, then in his first press conference Jan. 11, and again in an interview with the Washington Post published Jan. 16 – underscore the more complicated reality: the populist Republican President isn't backing down from claims that he will drive down drug costs.

Simply put, based on his public statements, Trump does not fundamentally differ in his views on drug pricing from his Democratic opponent (Hillary Clinton) – nor from his predecessor in the White House, Barrack Obama.

Like his predecessor, Trump says he favors Medicare price negotiation. Hearing a standard Democratic talking point coming from a Republican President is certainly reason for concern in industry. But it doesn't change the reality that there is no simple way to implement systemic price negotiation in Medicare, given the structure of the Part D benefit. (*See p. 9 for related story.*)

At the same time, it is also true that there is nothing to stop a suitably motivated Administration from finding ways to drive down prices one product at a time.

When "price negotiation" first became a rallying cry for Democrats, in fact, they cited actions by the GOP Administration under George W. Bush to "negotiate" a lower price for the antibiotic *Cipro*. That was a unique and complex story, but does illustrate the broader point: the bully pulpit is a powerful tool, one that can work even where laws are vague and uncertain.

Twitter attacks may be more efficient (and certainly more concise) than a series of Congressional hearings or a national coverage analysis, but many sponsors have learned that the lack of legal mechanisms to set prices does not mean that the federal government can't intervene in specific cases – as Turing Pharmaceuticals AG, Valeant Pharmaceuticals International Inc. and Mylan NV can attest.

Or, go back further and ask KV Pharma (*Makena*) or Dendreon Corp. (*Provenge*) or Idec Pharmaceuticals Corp. (*Zevalin*). If you can find them.

The fear of Trump using the bully pulpit of the White House to force companies to cut prices is very real. However, unlike so much about the Trump Administration, it isn't really new. In fact, it is something of an American tradition.

From the editors of The RPM Report.
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Industry Communications With Payors: US FDA Okays Info On Investigational Drugs

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FDA has taken a flexible position regarding the health care economic information that drug and device manufacturers may share with payors, permitting communication about investigational products and a range of information related to a product's approved indication.

In draft guidance, Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers, the agency describes the information on the economic consequences of the use of a drug that companies can share, the evidence needed to support the information, and details that should be included with it.

The guidance, released Jan. 18, is among a flurry of documents on communications about drugs the agency has issued in the last two weeks. The same day, FDA posted a memo on First Amendment considerations regarding communications about off-label uses of approved products. The memo largely lays out the agency's previously stated views and does not answer the question about what off-label information firms can provide.

On Jan. 17, the agency issued a draft guidance on communications consistent with approved labeling. And on Jan. 9 it revised its "intended use" regulations in a final rule on tobacco-derived drug products.

With these documents FDA "seems to be building an arsenal for what companies can do," Heather Banuelos, counsel at King & Spalding, said. "The agency is trying to clarify ways that companies may communicate additional information but still doesn't address the off-label question."

NEW SAFE HARBOR

The draft guidance on payor communications creates a new safe harbor from the prohibition on promotion of an investigational drug, as it allows companies to provide to payors certain information about investigational products prior to approval or clearance.

This information includes: factual presentations of results from clinical or preclinical studies; information about the indication sought, such as information from clinical study protocols about endpoints and the patient population; pricing; the anticipated timeline for possible FDA approval; marketing strategies; and product-related services, such as patient support programs.

FDA says the information must be unbiased, factual, accurate, and non-misleading and must be accompanied with a statement that the product is under investigation and its safety and effectiveness has not been established.

The guidance does not specify how early companies can provide information about investigational drugs.

Among other notable features in the draft guidance, Gillian Russell, also counsel at King & Spalding, said the guidance speaks to what it means for health care economic information to be "related" to a product's approved indication, defines the "competent and reliable evidence" standard, and outlines additional information and disclosures that must accompany health care economic information disseminated under the guidance.

SURROGATE ENDPOINTS, CLINICAL OUTCOME ASSESSMENTS

The FDA Modernization Act (FDAMA) of 1997 included a provision (Section 114) allowing manufacturers to share certain health care economic information not in product labeling with formulary committees. However, industry has been hesitant to do so without FDA guidance as to its interpretation of the statute.

The recently enacted 21st Century Cures Act amended the provision to clarify the types of information that can be disseminated under FDAMA and to whom. It extended the audience to include payors and similar entities and it changed the requirement that pharmacoeconomic information must "directly relate" to the approved indication to say that it only "relates."

Section 3037 of the 21st Century Cures Act states that health care economic information will not be considered false or misleading if, among other things, it "relates to an [approved] indication." The draft guidance provides examples of what information FDA considers related to an approved indication. The information includes analyses on duration of treatment; burden of illness; dosing; patient subgroups; length of hospital stay; validated surrogate endpoints; and clinical outcomes assessments or other health outcome measures, such as quality-adjusted year life.

Information that is not considered to be related to the approved indication includes analysis of disease course modification related to use of a drug that is approved only to treat symptoms of the disease.

The guidance defines the audience for health care economic information as payors, formulary committees (such as pharmacy and therapeutics committees), drug information centers, technology assessment panels, pharmacy benefit managers, and other multidisciplinary entities that review scientific and technology assessments to make drug selection, formulary management, and/or coverage reimbursement decisions on a population basis for health care organizations.

The guidance does not directly address FDA policy on communication of heath care economic information regarding unapproved uses of approved drugs. Instead, it refers to guidances FDA has is-

sued on how firms can respond to unsolicited requests for information on unapproved uses and disseminate scientific and medical publications discussing unapproved uses.

Kellie Combs, a partner at Ropes & Gray and co-counsel for the Medical Information Working Group (MIWG), said the guidance provides some clarity industry has long sought. The MIWG, a coalition of biopharmaceutical and medical device companies, submitted a memo to FDA in November 2014 on its interpretation of FDAMA's provision on health care economic information.

"We are encouraged that in many cases FDA adopted or agreed with the interpretation we laid out," Combs said, such as on the audience for the information and what information is related to the approved indication.

'COMPETENT AND RELIABLE SCIENTIFIC EVIDENCE' NEEDED

Michael Labson, a partner at Covington & Burling, said the draft guidance is consistent with changes from the 21st Century Cures Act and evolving case law on the First Amendment, and "provides additional important flexibility for manufacturers to communicate science-based information to payors."

Labson said the guidance "seems to articulate a relatively broad science-based standard." He noted that it appears to recognize that health care economic information could include treatment comparisons in the absence of head-to-head comparisons.

Addressing what evidence firms must have to support their health care economic information, the guidance states that FDA would not consider health care economic information to be false and misleading if it relates to an approved indication and is based on "competent and reliable scientific evidence (CARSE)." The guidance adds that Information would meet the CARSE designation if it was developed using generally-accepted scientific standards that yield accurate and reliable results.

The guidance states that when evaluating information based on indirect treatment comparisons in the absence of data from head-to-head controlled clinical trials, FDA may refer to guidelines issued by external expert bodies regarding methodologies and best practices for such comparisons.

The draft guidance notes that firms should also provide payors with information on the design of the economic analysis and the study objectives; the generalizability of the data; the limitations of the analysis; and a sensitivity analysis noting the uncertainties that could affect the conclusions. Firms must also provide information on differences in the health care economic information from the FDA-approved labeling, omitted studies or data sources, and important risk information.

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Mallinckrodt, FTC And The Antitrust Risks Of Pipeline Acquisitions

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The US Federal Trade Commission's $100m settlement with Mallinckrodt PLC over allegations that it purchased a product in development in order to keep a potential competitor off the market could make other firms more hesitant as they consider acquiring pipeline products to enhance existing franchises.

FTC had alleged that violated antitrust laws by purchasing the rights to Novartis AG's candidate *Synacthen Depot* (cosyntropin), a would-be competitor to Mallinckrodt's *HP Acthar Gel* (corticotropin). Acthar is the only adrenocorticotropic hormone (ACTH) drug on the US market.

In addition to payment, Mallinckrodt must grant a license to Marathon Pharmaceuticals LLC to develop Synacthen for FDA approval to treat infantile spasms and nephrotic syndrome within 120 days, according to the settlement announced Jan. 18.

Acthar was first approved by FDA in 1952 for the treatment of infantile spasms. It was acquired by Questcor Pharmaceuticals Inc. in 2001 from Sanofi. Questcor was later acquired by Mallinckrodt in August 2014. The year before, Questcor had purchased the US rights to develop Synacthen Depot, another ACTH drug, from Novartis in a $135 million deal.

FTC, however, alleges that by Questcor making the purchase, it "thwarted a nascent challenge to its Acthar monopoly and thereby harmed competition."

"Questcor's strategy to protect its monopoly position with Acthar was successful," FTC's initial complaint filed in the US District Court for the District of Columbia states. "But for Questcor's acquisition of Synacthen, one of the three alternative bidders would have acquired Synacthen and pursued its plan to develop Synacthen for [infant spasms] and/or [idiopathic membranous nephropathy] to compete directly with Acthar at a lower price."

Mallinckrodt didn't admit to any wrongdoing, noting that it had plans to develop Synacthen in the US for use in patients with Duchenne muscular dystrophy. The company announced in June 2016 that it had submitted an Investigational New Drug application for Synacthen with FDA for the indication.

"Synacthen Depot has never been FDA-approved for use in the US," Mallinckrodt said in a statement. "In fact, in all the time it has been commercially available, no owner (including the owner prior to Questcor) ever undertook US development in any indication until after the Questcor acquisi-

tion when Mallinckrodt began preparation for development in DMD."

FORMER CASES AND FUTURE IMPACTS

FTC tried to file charges against H. Lundbeck AS in a similar case in 2009 after the company acquired the only two products – *NeoProfen* (ibuprofen lysine) and *Indocin IV* (indomethacin) – to treat a congenital heart defect in premature babies. Although FTC argued that the acquisition resulted in higher prices and was anticompetitive, the court ruled that the drugs are not in the same product market.

Although Mallinckrodt didn't argue that Acthar and Synacthen are from different product markets, it did argue that synthetic ACTH products "are not especially complex to either formulate or manufacture at scale," adding that Synacthen and ACTH products have been on the market outside of the US for years. Synacthen, for example, is approved in Canada.

"Questcor claimed that it acquired Synacthen to develop it for new, non-Acthar indications, but given the drugs' similarities, any therapeutic indication that Questcor pursues with Synacthen could have been pursued with Acthar," FTC argues.

The direct impact of the monetary penalty likely won't be too big for Mallinckrodt, as the company took in $1 billion in net sales for Acthar in 2015. For other firms, the ruling may prompt them to reconsider product acquisitions that may be perceived by FTC a monopoly to avoid a lengthy court fight. The questions essentially seem to be how different does the product you want to acquire have to be from the ones you already have, and how much effort do you have to put into development in order to avoid an antitrust violation.

TIPPED OFF BY 'PHARMA BRO?'

Even with the broader implications of the settlement, one of the more interesting aspects of the case is a 2014 lawsuit against Questcor by Retrophin Inc., which was run at the time by none other than Martin Shkreli.

Shkreli, widely known by the nickname "Pharma bro" for his habit of smirking while price gouging, entered the spotlight in August 2015 when, as the CEO of Turing Pharmaceuticals AG, he raised the price of *Daraprim* (pyrimethamine) by more than 5,000% from $13.50 to $750 per pill after acquiring it from Impax Laboratories Inc. He was also CEO of KaloBios Pharmaceuticals Inc. before he was arrested in December 2015 on charges of securities fraud related to his time at Retrophin.

> Mallinckrodt didn't argue that Acthar and Synacthen are from different product markets, but did argue that synthetic ACTH products "are not especially complex to either formulate or manufacture at scale."

Retrophin filed suit against Questcor in January 2014, alleging the drugmaker swooped in and purchased Synacthen from Novartis when Retrophin already had a deal in place to purchase the drug, thereby impeding its ability to enter the ACTH market in the US.

According to Retrophin's complaint, the firm planned to obtain FDA approval for Synacthen and compete with Acthar by "dramatically undercutting Acthar's price." However, on June 11, 2013 – the day Retrophin says it was supposed to sign the agreement with Novartis – Questcor "swept in and acquired the rights to Synacthen. In doing so, it preserved and entrenched its ACTH monopoly in the US and eliminated the competitive threat posed by Retrophin's acquisition of Synacthen."

"The signing of the agreement was so imminent that a press release had been prepared to announce the deal," the complaint states. The complaint further alleges that Questcor did not make a Premerger Notification Filing with the Department of Justice and FTC as required by the Hart-Scott-Rodino Antitrust Improvements Act of 1976.

SHKRELI CRITICIZES HIGH DRUG PRICES

Knowing what we know now about Shkreli, Retrophin's complaint makes for a very ironic read as it criticizes Acthar's high prices. "[Questcor] has market and monopoly power in that market which is dramatically demonstrated by its continued ability to charge $28,000 for a vial of Acthar," the complaint states.

Although Shkreli may not have done anything illegal with his sharp price increase of Daraprim, he did take advantage of his position in the toxoplasmosis market, as there is no generic equivalent to Daraprim, despite being on the market since 1953. In fact, it's a product whose circumstances are not unlike Acthar, raising the intriguing possibility that Shkreli got the idea for his Turing strategy during his fight with Questcor.

Questcor and Retrophin reached a $15.5 million settlement in June 2015, but Shkreli's initial complaint may have tipped off FTC into investigating the transaction. According to an 8-K filing by Mallinckrodt, FTC issued a subpoena to Questcor on June 11, 2014, seeking documents and information related to Questcor's acquisition of Synacthen, roughly six months after Shkreli's complaint.

FTC also complained about Acthar pricing, though the settlement does not appear to directly address the issue. "Questcor took advantage of its monopoly to repeatedly raise the price of Acthar, from $40 per vial in 2001 to more than $34,000 per vial today – an 85,000 percent increase," FTC Chairwoman Edith Ramirez said in a statement. "We charge that, to maintain its monopoly pricing, it acquired the rights to its greatest competitive threat, a synthetic version of Acthar, to forestall future competition. This is precisely the kind of conduct the antitrust laws prohibit."

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Supreme Court Jumps Into Biosimilars Battle Over Launch Notification, Patent Dance

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The rules of the biosimilars pathway could change now that the Supreme Court has agreed to hear Amgen Inc. and Sandoz Inc. petitions challenging the Federal Circuit's interpretation of the statute. At stake is whether biosimilar sponsors must wait 180 days after approval to notify the brand-name company of intent to launch and whether the exchange of patent information is optional.

In orders issued Jan. 13, the court granted both Sandoz's petition on launch notification and Amgen's conditional cross-petition on the so-called patent dance provisions of the Biologics Price Competition and Innovation Act (BPCIA). The court consolidated the two cases, which involve Sandoz's *Zarxio* (filgrastim-sndz), a biosimilar to Amgen's *Neupogen* (filgrastim), and allotted one hour for oral argument.

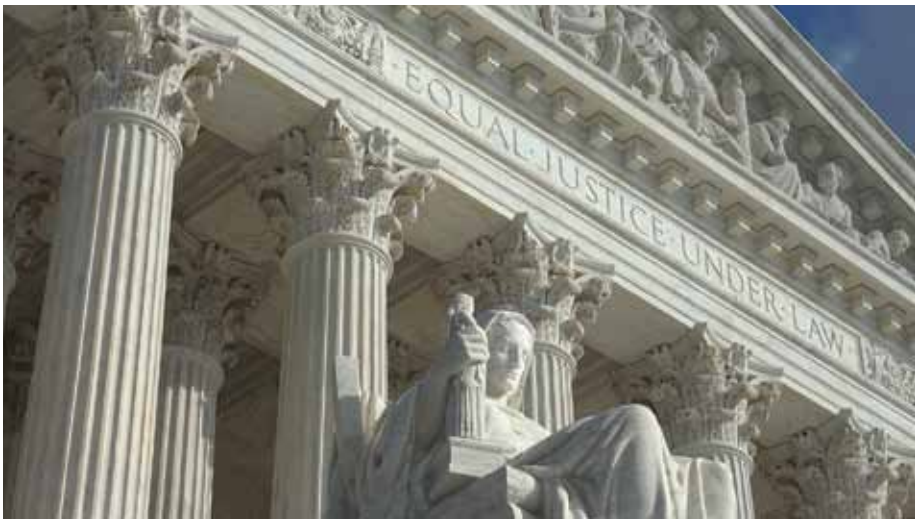
Sandoz and Amgen both issued statements saying they were pleased the court decided to hear their petitions and reiterating their interpretation of the statute.

Irena Royzman, a partner at Patterson Belknap Webb & Tyler, said the court recognizes that the case is very important to biosimilar sponsors and innovators. She said the question raised by Amgen is the more fundamental as it addresses whether the biosimilar sponsor can obtain the benefit of the biosimilar pathway and bypass the dispute resolution procedure.

The statute states that the biosimilar applicant "shall provide" its application and manufacturing process information to the reference product sponsor within 20 days after FDA's acceptance of its application for review. The US Court of Appeals for the Federal Circuit concluded that this did not mean the disclosure was mandatory since the statute provided consequences if the biosimilar sponsor failed to do so.

"Does 'shall' mean 'shall' is an attractive question for the court," Royzman said. "How it plays out is hard to know."

Royzman represents Janssen Biotech Inc. in litigation against Celltrion Inc. and Pfizer Inc. over their biosimilar to Janssen's *Remicade* (infliximab), *Inflectra* (infliximab-dyyb). She noted that it is also uncertain what the views of the new administration will be.



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DECISION IS LIKELY BY JUNE

The Solicitor General had advised the court to take up both petitions and sided with Sandoz on both the notification and patent dance questions. ([A#PS119656])

Acting Solicitor General Ian Gershengorn said the BPCIA requires the biosimilar sponsor to provide launch notice no later than 180 days before the date of the first commercial marketing but did not additionally restrict how soon the applicant may provide notice after submitting its abbreviated biologics license application to FDA. On the patent dance provision, he said the reference product sponsor could bring a declaratory judgement action against the biosimilar sponsor and obtain the information in discovery.

Goodwin Procter partners Robert Cerwinski and William Jay said the Supreme Court's decision to address questions about the statute will provide certainty about its application going forward.

"In this early stage of the biosimilars market it is something everyone is trying to figure out," Cerwinski said. "Given the dollars being invested in biosimilars it's important that industry gets certainty around these questions."

As for the timing of the case, Jay said the petitions were granted in time to be heard in April and the court will most likely issue an opinion by the end of the term in June.

COURT MAY ADDRESS APOTEX'S ARGUMENT

The case arose when Amgen filed suit against Sandoz, a unit of Novartis AG, for failing to follow the information exchange and notification provisions of the BPCIA, which provides a pathway for approval of biosimilars. Sandoz had not provided its BLA or manufacturing process information to Amgen and provided notification of its intent to launch Zarxio prior to approval.

In July 2015, a three-judge panel of the Federal Circuit ruled that the patent dance provisions of the BPCIA are optional and that Sandoz had to wait until FDA approval of Zarxio to notify Amgen of its intent to launch. However, the panel was divided as one judge dissented from the entire opinion and another dissented on the ruling regarding commercial notification. The

Federal Circuit denied petitions by both parties to rehear the case en banc.

In its petition to the Supreme Court, Sandoz argued that if the ruling is not reversed it will delay patient access to all biosimilars for six months longer than Congress intended.

Amgen opposed Sandoz's petition but asked the court to review the patent information exchange provisions of the BPCIA if it agreed to Sandoz's request.

Last month, the Supreme Court denied a petition by Apotex Inc., which also challenged the Federal Circuit's ruling on launch notification. Apotex argued that its case was different from that of Sandoz since it had provided Amgen with its application and manufacturing process information for a biosimilar to *Neulasta* (pegfilgrastim).

In its Jan. 13 orders, the court granted Apotex's motion to file a brief in the Zarxio litigation.

Royzman said she thinks the court will answer the questions in the case more broadly, in a way that encapsulates Apotex's argument based on its interpretation of Amgen v. Sandoz. "I would be surprised if the court didn't address these issues more holistically," she said.

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Biological Product Suffix Submissions Limited To 10 Candidates By US FDA

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The US FDA's plan to have sponsors submit up to 10 proposed suffixes for a biological product's distinguishable nonproprietary name should reduce the review burden on agency staff while also helping to ensure that a company gets one of its preferred suffixes approved instead of having the agency assign one.

In a final guidance released Jan. 12 on biological product nonproprietary naming, the agency requests sponsors of biologic license applications (BLAs) under Public Health Service Act Sections 351(a) and 351(k), as well as existing license holders, submit up to 10 proposed suffixes in their order of preference, with supporting analyses, for agency review.

The proposed suffixes must consist of a unique combination of four lower-case letters and be devoid of meaning. They must not connote the name of the license holder or be too similar to any other FDA-designated nonproprietary name suffix.

WORK ESTIMATE GREATLY INCREASED

The Office of Medication Error Prevention and Risk Management (OMEPRM), which currently oversees premarket reviews of proposed proprietary names of drugs and biologics, will also lead the nonproprietary name suffix reviews for biologic products in the Center for Drug Evaluation and Research.

In an interview, OMEPRM Associate Director Kellie Taylor said the agency has done a lot of thinking about how it will absorb the additional workload created by suffix reviews. She noted that the guidance contains different time points at which companies can submit proposed suffixes to help disperse the workload. (*See box)*

Taylor cited reasons of efficiency in the agency's decision to allow up to 10 submissions per product. This number is designed to avoid having multiple communications back and forth and resubmissions by a sponsor, which can bog down FDA reviewers and project management staff, she said.

The recommendation for 10 proposed suffixes is a change from an August 2015 draft guidance, in which the agency recommended that applicants submit no more than three proposed suffixes for review.

The agency signaled an upward shift in this number in June 2016, when it published a Federal Register notice pursuant to the Paperwork Reduction Act that stated the nonproprietary naming guidance recommended applicants submit up to 10 proposed fixes. The notice was withdrawn three weeks after publication. At the time, agency officials said the publication was an administrative error and that the figure of 10 submissions was likely used for purposes of estimating the burden on sponsors.

WHEN TO SEND FDA YOUR SUFFIXES

For Products Submitted Under Sec. 351(a):

- During the investigational new drug application (IND) phase or at the time of BLA submission; during IND phase should be submitted no earlier than at the request for a pre-BLA meeting.

For Products Submitted Under Sec. 351(k):

- During the IND phase or at the time of BLA submission; during IND phase should be submitted no earlier than at the request for a biosimilar biological product development (BPD) type 4 meeting.

For Retrospective Naming Of Products Licensed Under Sec. 351(a):

- Through a prior approval labeling supplement

However, with publication of the final guidance it now seems clear that the agency was set on increasing the number of suffix submissions long before the final document was publicly released.

In a Federal Register notice announcing the final guidance's release, FDA estimated an average burden of approximately 420 hours per sponsor to create and submit up to 10 proposed suffixes. This is the same hours burden that the agency included in the June 2016 notice that was subsequently withdrawn.

> "We tried to develop a naming convention that would minimize any potential for change to occur extrinsic to the license being sold." – FDA's Taylor

The current estimate is greatly increased from the initial estimate of six hours that accompanied the draft guidance. That number was based on a prediction that it would take sponsors two hours to complete a submission for each suffix, with a total of three suffixes.

However, that initial estimate "failed to adequately account for the time spent on creating proposed suffixes," the agency said.

Though increased, the current hours estimate is still well shy of the 720 hours predicted in one of the public comments on the original guidance, with the agency saying it believes that estimate "is likely too high."

The agency predicts that annually it will receive suffix submissions for 40 products submitted under Sec. 351(a) and six biosimilar products submitted under Sec. 351(k).

SAVING SUFFIXES FOR FUTURE USE

Despite support in industry and among other stakeholders for meaningful suffixes derived from a sponsor's name, FDA opted for suffixes devoid of meaning due to concerns about the potential for health care provider and patient confusion if there is a change in a product's license holder and, subsequently, in the suffix.

During a Jan. 12 stakeholder call to discuss the final guidance, Taylor was asked whether there were any circumstances in which an approved suffix would change, such as if a product is divested to another company.

"I wouldn't foreclose with absolute certainty the possibility that the suffix would change," Taylor said. "I think our current thinking … is that we tried to develop a naming convention that would minimize any potential for change to occur extrinsic to the license being sold, etc."

FDA officials also were asked whether the agency would issue an opinion on all 10 suffixes submitted by a sponsor or provide reasons why some suffixes were not acceptable.

"The idea would be that you'd list them in order of preference and our review is going to be complete on finding the first of the suffixes acceptable," Taylor said. "We would not proceed to review each and every suffix after that."

However, unreviewed suffixes lower on the sponsor's list could be used again by the same company for another submission, she said.

CAN FDA AND WHO NAMING SYSTEMS GET ALONG?

Although FDA is generally allowing sponsors to propose their own suffix, the agency announced plans in an August 2015 proposed rule to assign suffixes to a handful of previously approved products, including reference products for some of the early biosimilar applications submitted.

In addition, the guidance makes clear that FDA may assign a suffix at the time of BLA approval if an applicant does not submit a suffix the agency finds acceptable or does not proposed suffix candidates within an appropriate timeframe to allow for sufficient review.

The preference for allowing sponsors to propose their own suffixes is one key difference between the US regulator's approach and that of the World Health Organization's biological qualifier program. WHO's naming plan calls for a unique identification code consisting of four consonants and an optional two-digit checksum. The code would be randomly generated by WHO. Regulatory authorities may voluntarily adopt the system.

Beyond the source of the unique code or suffix, other differences between the FDA and WHO systems include that the US distinguishing suffix would be attached to the core name with a hyphen, whereas the WHO biological qualifier would follow the international nonproprietary name (INN) but would not be hyphenated.

In addition, distinguishable suffixes under the FDA plan would apply to the biological product, while the WHO biological qualifier would apply to the active substance.

WHO is piloting the program despite objections from some industry representatives.

Despite differences in the US and WHO systems, it's possible that some level of compatibility or alignment could be reached between the two systems.

For example, a sponsor that receives a WHO-generated code for a biological substance potentially could submit that code to FDA for review as a suffix for the biological product.

When asked about potential compatibility with the WHO program, FDA said it regularly engages with WHO's INN Programme and is working closely with the organization to understand technical aspects of its proposed naming policy.

"With respect to the compatibility of the two systems, while there are some differences between the WHO proposal and the FDA's naming convention, they both seek to assign an identifier to all biological products to improve pharmacovigilance and assist in the safe use of these products," the agency said. "We note that the WHO BQ would consist of four letters and be devoid of meaning and unique to each product, a construct that is similar to FDA's current thinking expressed in the final guidance."

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REMS Lawsuit Possible After US FDA Approves Generic Xyrem

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The US FDA could be facing a fight from Jazz Pharmaceuticals PLC after the agency approved a generic version of the company's narcolepsy drug *Xyrem* (sodium oxybate) with a Risk Evaluation and Mitigation Strategy (REMS) that uses multiple certified pharmacies and multiple databases for distribution.

FDA announced Jan. 17 that it approved the generic manufactured by Roxane Laboratories Inc., and Jazz didn't take long to denounce FDA's decision to waive the requirement that Xyrem and any generics use a single, shared system REMS. The drugmaker vowed it would explore its options to fight the decision.

"The Company will evaluate whether the FDA's waiver of the requirement for a single, shared system REMS in connection with approval of the ANDA meets the conditions for such a waiver under applicable law and, to the extent that the Company determines that the waiver was not permissible under applicable law, intends to evaluate potential challenges to the FDA's waiver decision," Jazz said in a Jan. 17 8-K filing to the Securities and Exchange Commission.

Approval of the generic, and Jazz's complaints about it, could put a spotlight on how risk management plans can sometimes delay generic competition. ANDA sponsors have long sought a legislative solution to the issue, but so far have not made much traction. The bill could garner more support, however, as the debate over drug pricing reaches a more heated stage.

For Xyrem, FDA spokesman Kris Baumgartner tells the Pink Sheet that although the REMS for the brand and the REMS for the generic "are comparable and are designed to achieve the same level of safety," there are some operational differences in the Elements To Assure Safe Use (ETASU).

The main difference is that the Xyrem REMS uses a single certified pharmacy for distribution and a single database to verify the safe use conditions required prior to dispensing the drug, while the Roxane's generic uses multiple certified pharmacies and multiple databases.

> The main difference between the two REMS programs is that the generic uses multiple certified pharmacies.

"The FDA has determined that this operational approach under the sodium oxybate REMS is comparable to, and is designed to achieve the same level of safety as, the Xyrem REMS," Baumgartner says. "In each case, the drug is shipped directly to the patient and not stocked on retail pharmacy shelves, the same patient counseling takes place prior to dispensing, and a required check from the certified pharmacy in the generic sodium oxybate REMS to the Xyrem REMS program is required to ensure that there have been no overlapping prescriptions, or disenrollments for diversion, abuse, or misuse."

As far as similarities, the REMS for the brand name and the REMS for the generic both require that:

- Prescribers of the drug are specially certified;
- The drug is dispensed only by specially certified pharmacies; and
- The drug is dispensed and shipped only to patients who are enrolled in the REMS program.

Both programs additionally contain the statement that the drugs "will not be stocked in retail pharmacy outlets."

Roxane, which is now owned by Hikma Pharmaceuticals PLC, did not immediately return a request for comment about the differences in the two REMS.

FDA'S DISPLEASURE WITH JAZZ

FDA previously approved an updated REMS for Xyrem in 2015 following a seven-year year negotiating process, but did so very reluctantly while voicing disapproval with Jazz' approach to the process.

Specifically, the agency took issue Jazz's argument that limiting dispensing to a single pharmacy is the only way to ensure that the benefits of Xyrem outweigh the risks. FDA noted that its approval with the REMS should not be construed as agreement with the single pharmacy approach, as it was concerned that it could block generic competitors.

The agency also pointed out that Jazz' insistence on a single-pharmacy system has not been a consistent argument, as the drugmaker had previously proposed using multiple certified pharmacies for Xyrem distribution in a 2009 supplement requesting to add a fibromyalgia indication. Jazz eventually received a complete response letter for the fibromyalgia indication.

Jazz made an additional attempt to halt generic competitors in September when it filed a citizen petition with FDA urging the agency not to approve any generic of Xyrem "with labeling that differs from that of Xyrem or with risk evaluation and mitigation strategies (REMS) that are not comparable to the Xyrem REMS Program."

The drugmaker specifically points to public court filings that it says indicate that at least one Abbreviated New Drug Application filer may be trying to omit portions of the Xyrem package insert and the Xyrem REMS that instruct prescribers to adjust the dose of the drug when co-administered with divalproex sodium.

"Omitting that information would render the generic less safe or effective than

Xyrem and, therefore, unapprovable under 21 C.F.R. § 314.127(a)(7)," the citizen petition states.

Jazz in its 8-K filing said that FDA approved the citizen petition Jan. 17 with respect to the Xyrem package insert. "The FDA concluded that it will not approve any sodium oxybate ANDA referencing Xyrem that does not include in its labeling the portions of the currently approved Xyrem package insert related to the drug-drug interaction with divalproex sodium," Jazz's SEC filing states. "The FDA stated that it did not need to reach the question of whether the drug-drug interaction information could have been excluded from the generic sodium oxybate REMS materials. The Company cannot predict whether or when one or more of the ANDA filers may pursue a challenge to the FDA's response to the Citizen Petition or whether any such challenges would be successful."

ONGOING PATENT LITIGATION

Also still in question is Roxane's ability to market the generic, as it is currently in an ongoing Patent fight with Jazz in the US Court for the District of New Jersey. Jazz sued Roxane in February 2015, alleging that Roxane infringed on three of its patents, including:

- Patent No. 8,461,203 titled, "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy;"
- Patent No. 8,772,306 titled "Method of Administration of Gamma Hydroxybutyrate with Monocarboxylate Transporters;" and
- Patent No. 8,859,619 titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy."

"Roxane's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration" of the patents "constitutes infringement of one or more of the claims" of the patents, Jazz's complaint states.

Roxane, however, contended in a motion to dismiss infringement count of the '306 patent that Jazz is attempting "to patent a law of nature." The patent covers the method of co-administering Xyrem with the anti-seizure medication divalproex sodium.

"Doctors routinely determine if a patient is taking other medications, and if so, recommend dosage adjustments," the motion to dismiss states.

Roxane also references the Supreme Court case Mayo *Collaborative Services v. Prometheus Laboratories, Inc.,* where the court held that certain patent claims are " patent-ineligible because they merely call for a doctor to adjust the amount of a certain drug administered to a patient depending on how that drug naturally acts in the human body."

Jazz previously sued Roxane in 2011, accusing it of infringing on a separate patent by attempting to obtain marketing approval for the drug. According to court documents, this case is not yet resolved.

Jazz has also been in a court battle with Amneal Pharmaceuticals LLC over Xyrem since 2013. Jazz accuses Amneal of infringing on six of its patents by attempting to obtain marketing approval. One of the six patents, however, was nixed by the Patent Trial and Appeal Board (PTAB) on the grounds of obviousness in July 2016.

PTAB also terminated five other Xyrem patents due to obviousness in cases brought by Amneal and Par Pharmaceutical. These other five patents, however, are separate from any of the patents in question that are undergoing litigation in court between Jazz, Roxane and Amneal.

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US FDA's Foreign Inspection Agenda: Visit The 1,000 Facilities It's Never Seen

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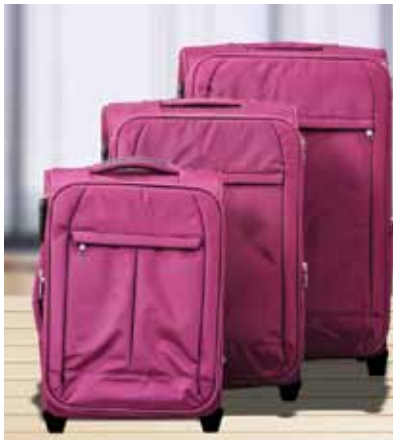

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Noting that FDA still has not inspected one third of the foreign manufacturing facilities that export pharmaceuticals to the US, the General Accountability Office urged the agency to do more to strengthen its overseas drug inspection program in a report released Jan. 17.

In particular, the congressional oversight agency encouraged FDA to better assess the effectiveness of its foreign offices and to set staffing goals for them. Responding on behalf of the agency, the Health and Human Services Department concurred in the recommendations and said FDA is already working to address them.

The report comes as Congress is yet again discussing drug importation legislation as part of the debate on Rx prices, and one can see it as bolstering either side: There's so much about foreign drug markets we don't know, an importation skeptic might note, but an importation proponent might ask how much risker the scheme could be if the regular channels already rely on suppliers that have never been inspected.

So far, though, political rancor has been noticeably absent from the report's release, with the House committee that requested it offering a bipartisan statement. "FDA has made some significant improvements over the last 10 years to their handling of the foreign drug inspection program, but more work lies ahead," Energy and Commerce Committee Chairman Greg Walden (R-OR) and Energy and Commerce Committee Ranking Member Frank Pallone, Jr. (D-NJ) said. "The gap in foreign drug firms that the FDA has no information on is sizeable and very troubling. Critical work remains, and with these recent improvements, … we're encouraged that these milestones can be reached."

GAO's count of FDA inspections of foreign drug establishments by country and year

COUNTRY	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016 (through June 30)	TOTAL
India	72	99	140	110	114	204	101	840
China	48	89	59	74	113	129	81	593
Germany	50	35	59	60	72	68	37	381
Canada	24	43	49	51	39	52	30	288
Italy	33	36	38	45	50	41	34	277
Japan	23	22	49	28	47	31	39	239
France	32	24	25	36	44	45	22	228
United Kingdom	16	31	29	27	33	43	18	197
Switzerland	26	30	23	23	37	31	16	186
Ireland	12	17	14	21	26	17	14	121
All other countries	104	133	140	161	204	181	111	1,034
Total	**440**	**559**	**625**	**636**	**779**	**842**	**503**	**4,384**

PROGRESS SEEN

GAO issued a landmark report eight years ago calling on FDA's inspectorate to turn its attention abroad.

That report came on the heels of a tainted heparin incident that revealed flaws in oversight of the global pharmaceutical supply chain and led Congress to enact supply chain regulatory reforms in 2012 as part of the FDA Safety and Innovation Act (FDASIA), which also renewed and expanded the agency's user fee programs.

The oversight agency acknowledged in its latest report that FDA has made much progress since its 2008 report and a 2010 follow-up that said the agency hadn't yet visited 64% of foreign manufacturing facilities that were exporting drugs to the US.

GAO said FDA has been increasing the number of foreign inspections each year – even reaching the point in 2015 of conducting more drug GMP inspections abroad than in the US. As of June, 2016 was looking to repeat that performance.

> "Beginning in fiscal year 2017, FDA will endeavor to revisit each of the 3,000 or so manufacturing establishments that export drugs to the US at least once every five years.

US-based investigators in FDA's Office of Regulatory Affairs have been conducted about half of the agency's foreign inspections, GAO said. The agency's US-based dedicated foreign drug cadre has been growing since it was established in January 2009, and now handles nearly a third of foreign inspections. Another 80 investigators hired with Generic Drug User Fee Act funds have only conducted 8% of foreign inspections during the period GAO reviewed, but their work volume increased significantly over the past two years. Meanwhile, investigators based in foreign offices have been involved in only 5% of foreign drug inspections, and staff on temporary duty assignments abroad have participated in just 2%.

A LEAP IN SURVEILLANCE

GAO documented a major change in the type of inspections FDA has conducted abroad over the past eight years, thanks to a FDASIA-mandated risk-based inspection scheme, the use of generic drug user fees and the retirement of a policy to limit foreign surveillance mainly to facilities receiving preapproval inspections.

Last fiscal year, the agency's Office of Regulatory Affairs finally combined domestic and foreign establishments into a single list, with funding priority set by the agency's risk-based site selection model.

Also, beginning in fiscal year 2017, FDA will endeavor to revisit each of the 3,000 or so manufacturing establishment that export drugs to the US at least once every five years. This initiative will start with a concerted effort to inspect the approximately 1,000 foreign establishments that the agency has never before visited.

FDA last year also established a formal governance structure for annual review and improvement of its site selection model. There is now a review board that tweaks the model's factors and weights based on input from subject matter experts.

STRATEGIC PLANNING ABROAD

FDA has made progress in strategic planning for its foreign offices since GAO last reported on them in 2010, the congressional oversight agency said. For instance, each office now has a quarterly-updated annual operational plan.

FDA has made progress on recommendations GAO made in 2010 to enhance foreign office strategic planning. There now are two performance measures in place: one for foreign inspections by foreign office staff and the other for collaborations with foreign regulatory authorities or other US agencies.

However, GAO said that even though FDA opened those offices in part to help increase foreign inspections, their staff have conducted relatively few inspections. From FY 2010 through Jun 30, 2016, the India, China and Latin America offices have only taken part in 241 drug inspections, GAO said.

And FDA chose to track all Office of International Programs collaborations rather than just those of the foreign offices, so it is not possible to see how much those offices collaborated. GAO also complained that FDA was unable to show how effective the foreign offices have been.

VACANCY RATE REMAINS HIGH

GAO urged FDA to work harder to fill vacancies in its foreign offices.

As of July 2016, 25 of 54 authorized full-time positions overseas, or 46%, remained vacant. The problem was worst in India, at 68%, followed by Latin America, 43%, Europe, 33%, and China, 32%.

GAO found that the agency was having particular difficulty filling certain positions. The vacancy rates were highest for international

FDA foreign drug establishment inspections increased as domestic inspections declined

	FY07	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	FY16 *
Foreign	333	324	424	440	559	625	636	779	842	503
Domestic	1,122	1,033	1,015	1,248	1,254	1,183	1,033	897	787	432

* FY 16 through June 30.

program policy analysts (60%), followed by investigators (55%).

In fact, 10 of India's 13 authorized investigator positions were vacant, for a 77% vacancy rate in the country that has become most identified in the minds of many for GMP violations.

"Given that one of the reasons for opening the foreign offices was to conduct inspections, the large number of vacant investigators is concerning," the GAO said, noting that in-country inspectors can reach sites more quickly and stay longer.

Some of the key factors in these high vacancy rates: the nine to 12 months required to complete overseas deployments; the likely hesitance to apply among FDA staff who have seen how difficult it is for returning foreign office staff to reintegrate into the agency's domestic offices; financial concerns associated with the lack of locality pay; environmental and security concerns; personal reasons; and unfamiliarity with FDA's global mission.

The agency has worked to reduce vacancy rates abroad by encouraging staff to apply for temporary duty rotations of one to four months abroad. About a quarter of those who took temporary assignments went on to work fulltime overseas.

GAO raised some concerns about the strategic workforce plan the Office of International Programs established in March 2016, complaining that it set an office-wide vacancy reduction plan instead of focusing on the overseas locations, which have the highest vacancy rates. There is a reintegration concept paper, but what the agency really needs are reintegration performance measures, GAO said.

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Manufacturers Urged To Prevent Drug Shortages By Reducing Quality Risks

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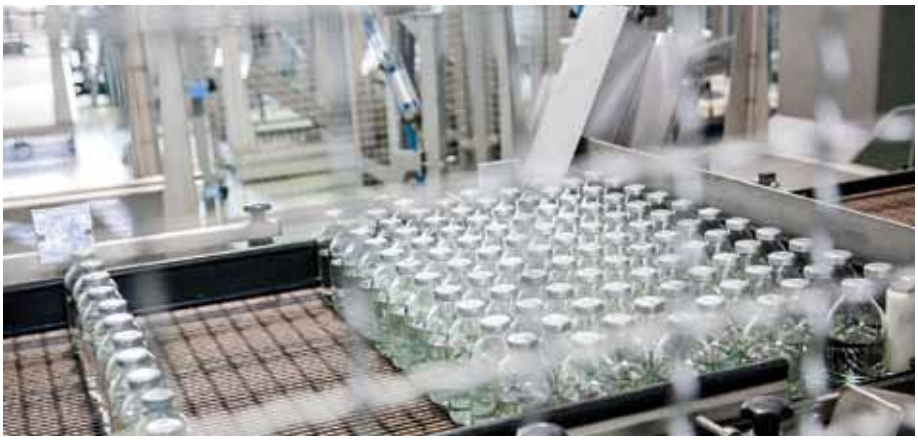

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Pharmaceutical manufacturers should work to prevent drug shortages by averting quality failures that could trigger them, a Jan. 12 report from the Pew Charitable Trusts and the International Society for Pharmaceutical Engineering concludes.

The report recommends the use of periodic risk assessments, which identify potential compliance risks across a company's supply chain, and trending reports that can help forecast potential problems and supply disruptions early on.

The report's findings are based on a survey of more than 50 executives from 10 companies that collectively manufacture a mix of branded, brand-generic and generic drug products. The report focused on manufacturers of sterile injectable drugs, which are the most vulnerable to supply disruption and some of the most technically challenging drug products to manufacture.

The report builds on a 2013 drug shortage survey which found that the reasons for drug shortages are multi-factorial and multidimensional.

According to the General Accounting Office, there were 456 drug shortages from 2011 to 2014 and the situation is "static or worsening." Of the shortages, more than 72%, were in the sterile injectable category, and the affected product categories or therapeutic classes ranged from anti-infective and anesthetic drugs to cardiovascular and oncology treatments.

The survey respondents said that quality issues are the primary contributor to shortages. Of the 29 reference products reviewed for the report, 13 or 45% experienced shortages due to quality issues. The report defines quality issues as a combination of good manufacturing practice compliance violations as well as product development or manufacturing problems that led to lower than expected product yields.

Some of the specific quality issues that led to drug shortages at sites:

- A product's active pharmaceutical ingredient manufacturing site was subject to quality gaps that caused a delay in production;
- A contract manufacturing site did not follow GMP regulations;
- The transfer of a legacy product to a new manufacturing site was held up by delays in developing and transferring the requisite analytical methods.

Respondents from nine companies said they had systems in place to communicate risks to quality across the manufacturing fa-

cilities. The report said, however, that these systems were "reactive in nature, reporting only issues that had already occurred."

The report said that a more proactive approach is needed to forecast potential shortages, and recommended the use of periodic risk assessments to identify potential compliance risks across a company's supply chain, as well as the use of trending reports that review past supply chain data trends to forecast potential issues.

Manufacturers identified other reasons behind drug shortages, including the inability to ramp up production when a competitor leaves the market. Other factors cited were lack of purchaser manufacturer incentives.

Representatives were also asked what business strategies they have in place to prevent drug shortages. All said they maintain buffer or extra stocks of raw materials such as excipients and vials needed to meet rapid and unexpected increases in product demand; they all say they store backup inventory of finished products at their packaging sites to protect against unexpected product demand.

Nine companies reported using backup external manufacturing facilities in the event of a shortage while eight have second-source suppliers to provide components, vials, stoppers and raw materials in the event of a shortage.

Manufacturers said, however, that sometimes these contingency plans can fail when backup suppliers have quality problems of their own "suggesting that manufacturers need to do a better job of measuring and monitoring the quality system that they and their suppliers use to guard against such failures."

To reduce shortages, the report also recommended the use of guaranteed utilization orders. Eight companies said that if group purchasing organizations, or GPOs, were to provide a guaranteed order or a commitment to order a specific amount annually to manufacture lower-margin lower-volume products, shortages could be reduced for these products, especially those without predictable demand.

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India Pharma 2017: 3Cs And D (Disruption)?

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Brace for action on various fronts in the Indian pharmaceutical industry and possibly some disruption too – that's the general forecast for 2017 according to a number of industry experts.

While price-related headwinds cannot be wished away, compliance, collaboration, and maybe a dash of consolidation are some of the prominent themes that are seen playing out in the new year. Some top executives are hopeful that the Narendra Modi-led government will plough deeper with its much publicized "ease of doing business" initiatives.

"I expect that a number of regulations are likely to be re-examined and simplified in multiple domains across the pharmaceutical sector," Novartis India country president Jawed Zia told Pink Sheet.

The key events that the Novartis president hopes will play out include an easing of restrictions on local clinical trials that will facilitate faster launches of innovative pharmaceutical products, and "considerable acceleration" in collaboration between innovative research-based companies and local generics firms.

The latter, he emphasizes, will help broaden reach and be a win-win for all

"I expect that a number of regulations are likely to be re-examined and simplified in multiple domains across the pharmaceutical sector," Novartis's Zia said.

stakeholders. Novartis itself has a few alliances with local firms for products such as vildagliptin in India.

Industry veteran Ajit Dangi, president and CEO of Danssen Consulting and a former director general of the Organization of Pharmaceutical Producers of India (OPPI), which represents foreign firms in India, also sees a harmonization of certain Indian regulatory guidelines with those of the developed world.

"We have already seen this in case of clinical trials and biosimilar guidelines. On the intellectual property rights [IPR] front, however, we have a long way to go," Dangi, also a former president and executive director of Johnson &Johnson India, told Pink Sheet. Then there is action anticipated around rising quality standards, which would require better enforcement and Zia suggests that this is, in turn, will lead to consolidation in the sector either by way of acquisitions of companies or brands or by collaborations.

"Either way this will be good for the industry," Zia said.

COMPLIANCE

An uptick in compliance related activities – both oversight by Indian and foreign regulators and a greater focus in the area by companies in India – is anticipated in 2017.

Novartis's Zia said that compliance has come to stay and will continue to be in focus; he also hopes that a "well-balanced and pragmatic" Uniform Code for Pharmaceuticals Marketing Practices (UCPMP) that is "implementable" will be made mandatory in India.

"Indian companies export a significant amount of their turnover and so they will have to focus on compliance to stay competitive. Companies will continue to invest on compliance-related initiatives both internally and externally," he says.

Viren Mehta, managing member of Mehta Partners LLC, a strategic business advisory, told Pink Sheet that 2016 has been a better year for the Indian industry, where the number of warning letters and import alerts from the FDA for Indian sites declined as compared to 2015.

"Indian pharma companies demonstrated strong improvement on the global regulatory front, as the number of warning letters (8 vs.12) and import alerts for Indian sites (3 vs.12) in 2016 versus 2015 is a noteworthy positive. This demonstrated progress will continue," Mehta declared.

"An uptick in compliance related activities – both oversight by regulators and a greater focus in the area by companies in India – is anticipated in 2017.

He also observed that in 2015-16, regulators, mainly the US FDA, stepped up the frequency of checks, demanding stricter compliance, leading to a higher number of Form 483 issuance rates versus the past. A Form 483 is a notice of the FDA's inspectional observations that lists deficiencies in quality systems.

GLOBAL EVENTS

Mehta also referred to a series of global events/ trends that could impact Indian firms in 2017, including the evolving geopolitical situation and the impact of US channel consolidation versus faster approvals through the GDUFA (Generic Drug User Fee Amendments) system.

"[US President-elect Donald] Trump and [Angela] Merkel are on top of most of the lists, but the legislative agenda across the EU, Japan, the US as well as many other important markets bears watching," Mehta said.

He notes how channel alliances/consolidation in 2016 (Walgreens-Rite Aid, McKesson-Walmart) will continue and impact the US generics market, including higher volume discounts and higher working capital needs, challenging margins.

"The companies with high profits from the US (such as Aurobindo Pharma Ltd., Zydus Cadila) may have better foundation to weather the impact. Late entrants (such as Torrent Pharmaceuticals Ltd., Strides) have benefited greatly from GDUFA, attracting other competitors, and this trend should continue in 2017."

There have been certain significant advances by Indian firms in the biosimilars segment too. Mehta notes that a handful of Indian companies invested "wisely", and "their patience should be rewarded" in 2017, as the US biosimilar market opens further.

"The challenges around biosimilar development, regulatory pathways, ongoing patent litigation, remain, and are costly. Hence alliances with multinational companies and selected smaller companies will play an important role."

Biocon Ltd. and partner Mylan NV last year announced the submission to the US FDA of a biologics license application (BLA) for a proposed biosimilar trastuzumab through the 351(K) pathway; Europe's EMA has also accepted for review the duo's marketing authorization application for their proposed biosimilar *Herceptin*.

On Jan 11, the partners said that the FDA had accepted Mylan's BLA for the proposed biosimilar trastuzumab and that the anticipated FDA goal date set under the Biosimilar User Fee Act (BsUFA) is Sept. 3, 2017.

MERGERS AND ACQUISITIONS

Most experts also see a continuing trend of mergers and acquisitions (M&A) and divesture of tail-end, mature brands by innovator firms which could potentially attract Indian interest.

Dangi emphasized that with over 10,000 pharma manufacturers and an "intensely" fragmented market, a "strong dose" of consolidation to increase the scope and scale of economies is "badly needed".

"M&A deals as well as in/out-licensing to focus on core strength and shedding mature brands with low profitability and market share is likely to pick up steam," he says.

Mehta suggests that the increasing desire for specialty and orphan pharma

products will attract complex injectable generics and repurposed molecule opportunities. He claims that Mehta Partners conceptualized and realized the mature product divestment opportunity with the Novartis-Sun transaction and expects many to follow this "creative trend".

2016 saw a series of transactions involving Indian firms including Intas Pharmaceuticals Ltd. acquiring certain Teva Pharmaceutical Industries Ltd. assets in Europe, Lupin Ltd.'s acquisition of a basket of long-listed products from Shionogi & Co. Ltd. in Japan.

In March 2016 Sun Pharmaceutical Industries Ltd. acquired certain established Novartis AG brands in Japan.

DISRUPTION

But beyond the traditional action areas, experts caution that industry should probably also factor in some disruption.

Dangi says that as the Indian economy begins to get integrated with the global economy and enters the digital era, "radical" changes are likely to take place in the business environment oft described by the acronym VUCA (volatile, uncertain, complex and ambiguous).

"Brexit, the Trump presidency, Indian demonetization, the Tata corporate feud (the group is locked in an acrimonious public battle against the ousted chair Cyrus Mistry) and India's proposed GST (Goods and Services Tax) regime have shown that the disruption is the new normal," Dangi said.

On Nov. 8, India scrapped its two largest denomination currency notes as part of efforts to flush out "black money" (essentially illegally obtained or not accounted for tax purposes), fight corruption, cripple terror financing and check counterfeit notes.

Mehta suggests that one thing that is certain about the new Trump administration is uncertainty.

"Let us add another word, inconsistency. Best strategy will be flexibility and opportunistic preparedness to adapt as the landscape evolves," he advised.

Dangi said that while disruptions such as the ban on fixed dose combinations, US FDA compliance issues and an increasing span of price controls will have some impact on the business of domestic firms, factors such as the increase in disposable income, rise in life style diseases, increasing healthcare penetration and in government spend on healthcare and insurance, and expected corporate tax reforms, in the forthcoming India budget will all positively impact industry.

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FDA's ANDA Approvals

SPONSOR	ACTIVE INGREDIENT	DOSAGE; FORMULATION	APPROVAL DATE
Panacea	Rizatriptan benzoate	EQ 5 mg base and EQ 10 mg base; orally disintegrating tablet	1/11/2017
Orit	Bisoprolol fumarate	5 mg and 10 mg; tablet	1/11/2017
G&W Labs	Triamcinolone acetonide	0.1%; dental paste	1/12/2017
Zydus	Methotrexate sodium	EQ 2.5 mg base; tablet	1/13/2017
Apollo	Piperacillin sodium/ tazobactam sodium	EQ 2 gm base/vial/EQ 250 mg base/vial, EQ 3 gm base/vial/ EQ 375 mg base/vial and EQ 4 gm base/vial/EQ 500 mg base/ vial; injection	1/13/2017
Apollo	Piperacillin sodium/ tazobactam sodium	EQ 36 gm base/vial/ EQ 4.5 gm base/vial; injection	1/13/2017
West-ward	Sodium oxybate	500 mg/mL; oral solution	1/17/2017
Tentative Approvals			
Glenmark	Olmesartan medoxomil	5 mg, 20 mg and 40 mg; tablet	1/13/2017
Aurobindo	Ritonavir	100 mg; tablet	1/13/201
Accord	Quetiapine fumarate	50 mg; extended-release tablet	1/18/2017

Guidance On Acetaminophen Allergy Warning Trails Industry's Change

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An FDA final guidance recommends a skin allergy warning on OTC monograph acetaminophen products that the Consumer Healthcare Products Association contends should be made in more formal rulemaking, even though most of the products now marketed already include the language.

The agency did not agree with CHPA's contention and on Jan. 11 published a final guidance with a recommended warning and labeling statements regarding serious skin reactions for acetaminophen-containing products marketed under the tentative final monograph for internal analgesic, antipyretic and antirheumatic (IAAA) OTC drugs.

However, the final guidance also adds an example the trade group suggested for a warning to use with labeling for a product containing both acetaminophen and aspirin. The separate language was needed to highlight differences in location of the "Allergy Alert" and "Liver Warning" statements between single-ingredient products and those containing both ingredients.

CHPA acknowledges that FDA did not agree with its suggestion for a rulemaking, but says the IAAA TFM itself still is not finalized.

"We remain committed to working with the agency to ensure finalization of rulemaking proceedings on the remaining TFMs," said Jay Sirois, CHPA's director for regulatory and scientific affairs, in an email.

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Drug Facts Panel, Warning Section

On the Drugs Facts panel of product labels, this statement is recommended for the Warnings section:

Allergy alert:
Acetaminophen may cause severe skin reactions. Symptoms may include:

- **skin reddening**
- **blisters**
- **rash**

If a skin reaction occurs, stop use and seek medical help right away.

NDA ACETAMINOPHEN OTCS CAME FIRST

The guidance is the Center for Drug Research and Evaluation's latest step to increase consumers' safety in using acetaminophen-containing OTCs by making known the risk of rare but serious skin reactions – including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis – that can be fatal.

CDER in 2013 warned consumers about the risk and also began working with manufacturers of acetaminophen OTCs approved through new or abbreviated drug applications to add warnings. A review of medical literature and the FDA Adverse Event Reporting System found 107 cases from 1969 to 2012, including 12 deaths, that identified the ingredient as a "probable" or "possible" cause.

"At this time, all of the required labeling changes and most of the requested labeling changes [for NDA acetaminophen OTCs] have been made by the relevant manufacturers," CDER states in the final guidance.

The center notes that in 2013 it also indicated that it planned to encourage firms marketing acetaminophen monograph OTCs also to add the skin reaction warning, which it did in a late 2014 draft guidance.

CHPA supports adding label warnings, but said in its 2015 comments on the draft guidance that the label changes FDA suggested should be proposed in a rulemaking to change the OTC monograph. The trade group commented that many of its members already were adding a warning for serious skin reactions to the Drug Facts panels for acetaminophen-containing products, with text that mirrors the warnings suggested in the draft.

Adding a label warning to an OTC monograph would make the change mandatory for all manufacturers marketing drugs under a monograph, leaving no room for argument should FDA enforce against a product that does not include the warning. However, industry stakeholders periodically argue that FDA requires firms marketed regulated products to comply with its expectations stated in guidances, rather than with requirements explicit in regulations.

CDER explains in the final guidance that although the recommended warnings are not part of the TFM, the agency currently will exercise enforcement discretion for labels that include the warnings.

"At this time, FDA does not intend to take action against the marketing of products containing the" recommended allergy warning language "as long as those products are otherwise marketed in compliance with the TFM and applicable regulations," the guidance states.

CDER also notes the discretion does not extend to "alternative allergy warning language that may otherwise misbrand the product."

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Recent And Upcoming FDA Advisory Committee Meetings

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

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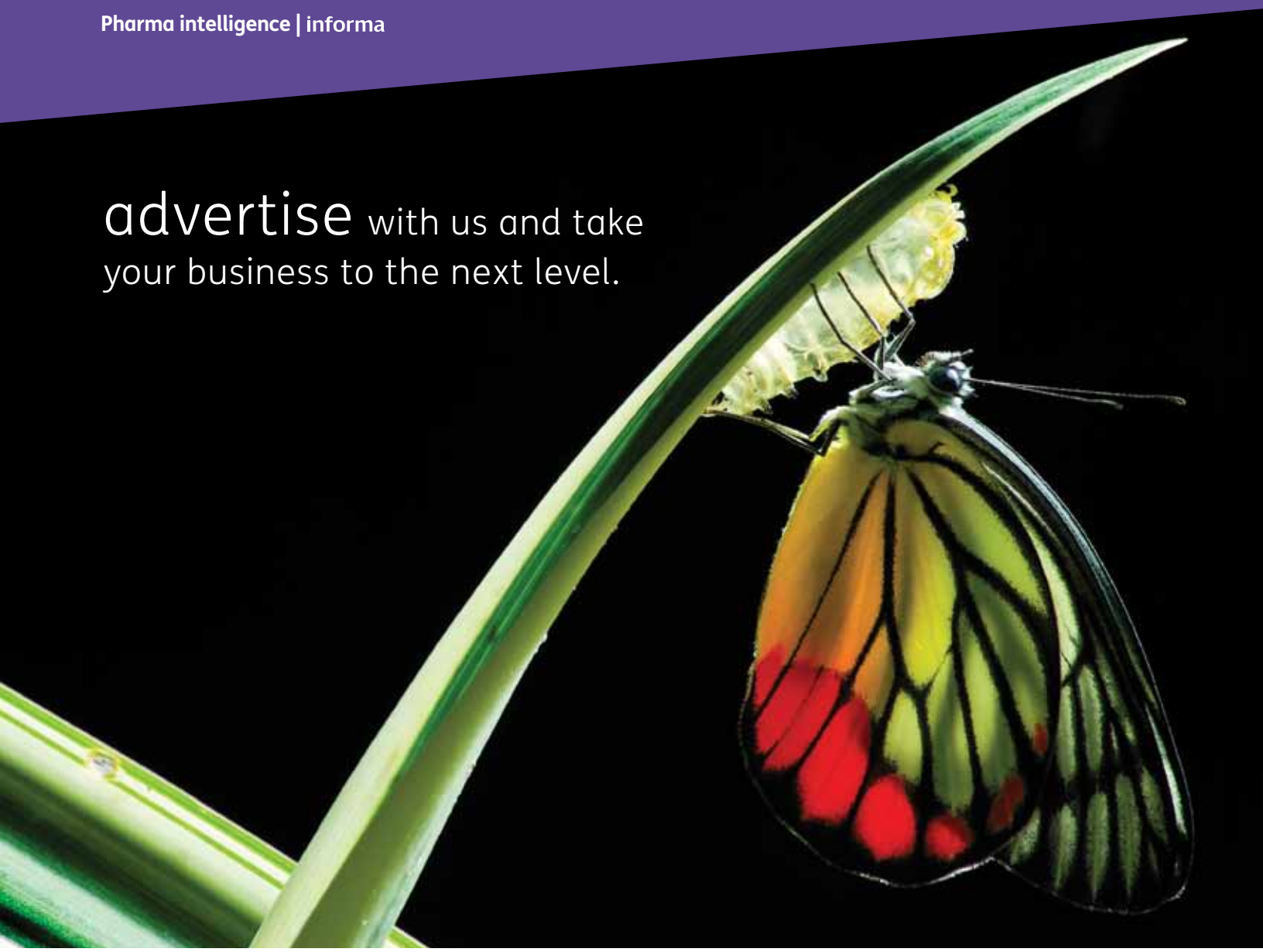

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