Pink Sheet
pink.pharmaintelligence.informa.com Vol. 79 / No. 51 December 18, 2017
Pharma intelligence informa

# DRUG PRICING: US House, Senate, Taking Bicameral Go-Slow Approach

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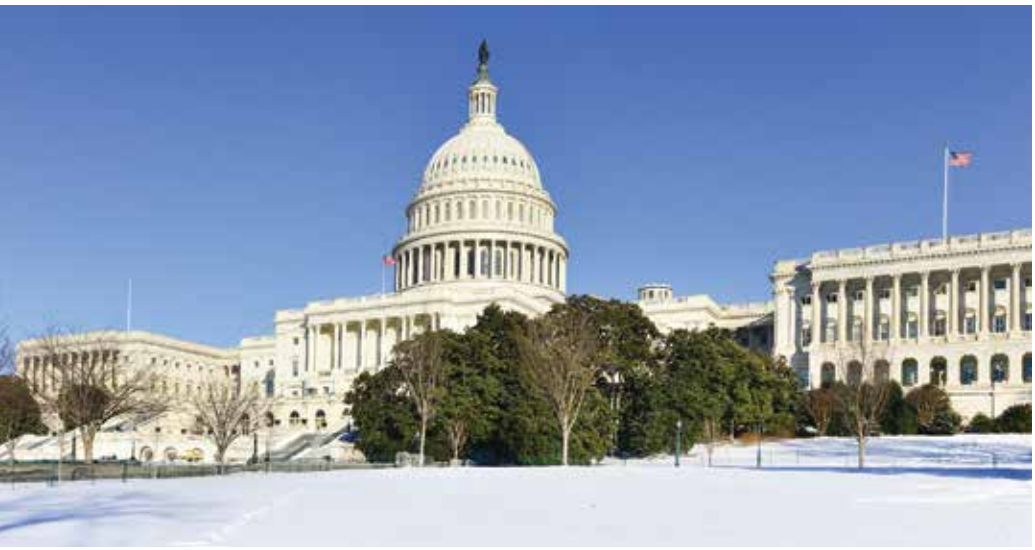

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The US House Energy & Commerce Health Subcommittee won't be rushing into any legislative action on prescription drug pricing, leadership signaled at a Dec. 13 hearing on prescription drug pricing and the supply chain.

Comments by committee Chairman Greg Walden, R-Ore., and subcommittee Chairman Michael Burgess, R-Tex., indicated that the House is unlikely to move any faster than the Senate in developing legislation to lower drug prices. *(Also see "Drug Pricing: US Senate Hearings Conclude With No Clear View On Legislation" - Pink Sheet, 12 Dec, 2017.)*

Walden and Burgess framed the hearing as the beginning of an information-gathering process that would take time.

"We are here today to learn from patient and industry experts and improve our understanding of the drug supply chain," Walden said in prepared opening remarks. "In order to fully appreciate the drug supply chain, you have to acknowledge its complexity and ask questions instead of jumping to conclusions. I encourage members on both sides of the aisle to dismiss any preconceived notions."

Walden added that "for me, this isn't a drug pricing hearing. There's enough rhetoric about the cost of drugs. But having said that I know that I have more to learn about the impact each participant in the supply chain has on the ultimate cost to patients."

Burgess echoed in his opening statement that "today's hearing will serve as an important educational opportunity to better understand the intricacies of our nation's drug supply chain."

During the hearing, Walden pushed back against the suggestion by some subcommittee Democrats that the panel form a working group to focus on drug pricing issues, which could accelerate a move toward legislative action.

"That is the job of this subcommittee," Walden emphasized. "We are going to do regular order right here on the Health Subcommittee." He added "there may be an opportunity to come back after the first of the year and continue this discussion. … But the notion that there's going to be a splinter group go off and do something – put a nail in that one."

The subcommittee assembled an impressively large panel for its hearing, with 10 health care stakeholders sitting at the witness table together. But the exercise only showcased the lack of consensus among the players as to who is responsible for high prices and what to do about it.

"There is a lot of finger pointing going on but I will tell you all I think there is more than enough blame to go around for what we see transpiring in the marketplace," Rep. Marsha Blackburn, R-Tenn., observed. "This is an issue that we need to address and we need your best efforts at solving this."

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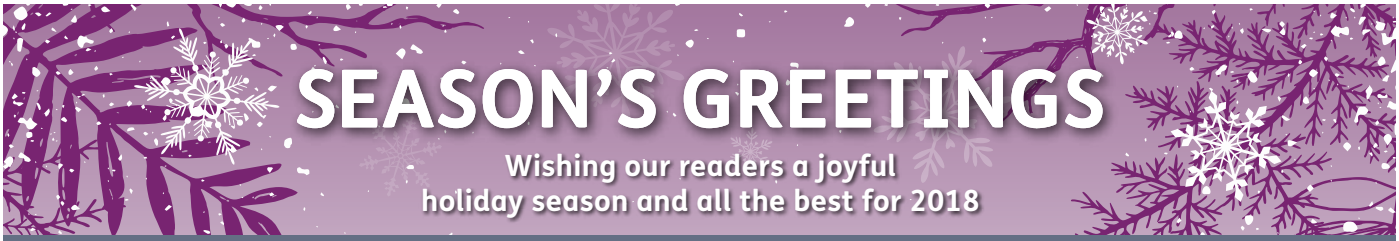


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## exclusive online content

**Lilly, Novartis, Jazz and Ionis Take New Products To EMA**

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Lilly's migraine prevention therapy, galcanezumab, is among the nine new products that companies have submitted to the European Medicines Agency for evaluation in recent weeks.

**Value-Based Contracts Getting More Safe Harbor Attention From OIG**

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But so far, OIG has declined a blanket safe harbor for proposed value-based payments, saying it still wants to consider proposals case-by-case. Discussions between the office and stakeholders are continuing, Bristol-Myers Squibb's Mike Ryan says.

**EU Guideline On Investigational ATMPs Delayed Until Q3 2019**

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Several factors have contributed towards a delay in the European Medicines Agency's much awaited guideline on investigational advanced therapy medicinal products, which was initially due to be finalized in the second quarter of 2017.

**Brexit Could Rob Industry Of Access To Markets Covered By 35 EU Free Trade Deals**

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A coalition of life sciences industry bodies has written a position paper outlining its concerns about Brexit in areas such as EU free trade deals, customs declarations and tariff barriers.

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# inside:

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She asked each witness to briefly identify "what changes you would like to see in the marketplace or what changes to the law should we make to make certain that… we're focusing on access, delivery and the cost of these pharmaceuticals to patients."

There were recurrent themes among the answers she got from witnesses, including action to hasten generic and biosimilar competition and pricing transparency, particularly involving pharmacy benefit managers. (*See box.*) But there were many areas of disagreement.

## STAKEHOLDERS SHOULD DEVELOP CONSENSUS ON SOLUTIONS

Rep. Morgan Griffith, R-Va., suggested greater transparency about PBM contracting activities could resolve who is to blame. "I think we have got to have some transparency so that the average person in the US understands why it is that you all are up to here pointing fingers at each other, and it all comes back to what's going on inside that big black box, which is the PBMs."

But he also remarked that consensus is lacking. "Everybody is saying 'this is the problem' or 'that is the problem' but … I believe you all need a working group because if you don't solve this we might have to come up with an answer and it may not be an answer that you end up liking."

Subcommittee Chair Burgess similarly urged that stakeholders should work on a market-based solution. "You're smarter at this stuff than we are by a lot and you may have some solutions that you can arrive at … in collaboration. I would submit to you that these solutions may well be better than anything we or a federal agency can impose."

He warned there will be action on drug pricing, eventually. "If we're not moving toward some solutions to this problem, then there likely will be some action taken – perhaps not by this subcommittee this year, perhaps not by this subcommittee next year – but there will be action taken, whether by an agency or legislatively."

*Published online December 13, 2017*

"I think we have got to have some transparency so that the average person in the US understands why it is that you all are up to here pointing fingers at each other, and it all comes back to what's going on inside that big black box, which is the PBMs." – Rep. Griffith

## HOUSE SUPPLY CHAIN HEARING WITNESSES: QUICK TAKES ON DRUG PRICING SOLUTIONS

- Pharmaceutical Research and Manufacturers of America: Pass through discounts and rebates to patients to reduce cost sharing and move toward a value-based system that rewards manufacturers for producing the outcomes patients and payers want.
- Biotechnology Innovation Organization: Empower patients with better information about formularies, cost sharing.
- Association for Accessible Medicines: Repeal the Medicaid price inflation penalty rebate for generics; pass the CREATES Act that targets practices aimed at blocking development of generics; include biosimilars in 50% coverage gap discount program in Part D.
- Pharmaceutical Care Management Association: Promote value-based contracting; implement patent reforms that enable faster generic competition; promote e-prescribing that would provide prescribers with information about formulary costs in advance.
- Healthcare Distribution Alliance: Anything that examines greater competition and access for patients.
- America's Health Insurance Plans: Advance solutions that bring more competition from generics and biosimilars; promote greater transparency over how prices are set and why they increase; and move toward value-based and outcomes-based pricing.
- American Medical Association: Promote transparency and eliminate administrative hassles that hamper care delivery.
- National Community Pharmacists Association: Promote transparency around PBM spread pricing, or what the pharmacy is paid and the employer is charged; restrict direct and indirect remuneration; and eliminate the conflict of interest between the price giver and price taker.
- American Hospital Association: Promote greater transparency; pass the CREATES Act; protect the 340B program.
- Patients for Affordable Drugs: Make the Hatch-Waxman Act work as intended, including by prohibiting pay-for-delay settlements or other actions that extend patents beyond what the law intended; pass the CREATES Act.

# Sanofi's Admelog, a Humalog Follow-On, Approved In US As 'Black Hole' For Insulins Looms

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**Sanofi** will launch *Admelog* (insulin lispro injection), the first short-acting insulin follow-on product approved in the US, in early 2018, but the product faces an uncertain regulatory future given the looming effective date of the Biologics Price Competition and Innovation Act's (BPCIA) "transition provisions" for insulins and other protein products.

FDA granted final approval to Sanofi's new drug application (NDA) for Admelog, a follow-on to **Eli Lilly & Co.**'s *Humalog*, on Dec. 11 for glycemic control in adult and pediatric patients three years and older with type 1 diabetes and adults with type 2 diabetes.

"With today's approval, we are providing an important short-acting insulin option for patients that meets our standards for safety and effectiveness," Mary Thanh Hai, deputy director of FDA's Office of Drug Evaluation II, said in an agency press release. Thanh Hai is heading up the Division of Metabolism and Endocrinology Products on an acting basis in light of the announced departure of Division Director Jean-Marc Guettier for a job in the private sector. *(Also see "FDA Endocrinology Division To Be Led By Thanh Hai On Interim Basis; Guettier Leaving For Private Sector" - , 8 Dec, 2017.)*

Sanofi's product was approved through the 505(b)(2) NDA route, which allowed Sanofi to rely on FDA's previous findings of safety and efficacy for Humalog. The sponsor also submitted Admelog-specific data to establish safety and efficacy, including two Phase III trials that enrolled approximately 500 patients each.

These trials, SORELLA 1 and 2, also supported the marketing authorization granted by the European Commission in July, which followed a positive opinion in May from the European Medicines Agency's Committee for Medicinal Products for Human Use. *(Also see "All Set For EU Approval: First Biosimilar Humalog And Three More Rituximabs From Celltrion" - , 19 May, 2017.)*

## EXCLUSIVITY TO BE REDUCED BY ONE-FOURTH?

Given the 505(b)(2) pathway used for FDA approval, Admelog is not considered a true generic. However, the product also is not considered a biosimilar because insulin products traditionally have been approved as new drugs under the Food, Drug and Cosmetic (FD&C) Act.

This regulatory paradigm will change come March 23, 2020 thanks to the BPCIA transition provisions. On that date, insulin, human growth hormone and certain other protein products traditionally regulated under the FD&C Act will be deemed to be licensed as biological products under Section 351 of the Public Health Service (PHS) Act.

In a March 2016 draft guidance explaining how the agency intends to implement the provisions, FDA said transition products that have not received final NDA or abbreviated new drug application approval by March 23, 2020 will not be approved under the FD&C Act and must be resubmitted as biologic license applications (BLAs) under the PHS Act.


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> Under FDA's current policy, Sanofi would lose almost nine of its 36 months of Hatch-Waxman exclusivity when the transition provisions take effect March 23, 2020.

Products that were approved under the FD&C Act before the transition date, such as Admelog, would lose any remaining marketing exclusivity, except for orphan drug protection, on the transition date, according to FDA's guidance. Such products would not be entitled to the 12-year exclusivity that biologics receive when initially licensed as standalone BLAs. *(Also see "BLAs More Appealing As 'Transition' NDAs, ANDAs Set To Lose Exclusivity" - Pink Sheet, 21 Mar, 2016.)*

Admelog appears positioned to pick up three-year, new product exclusivity under Hatch-Waxman because Sanofi conducted new clinical studies necessary to support the approval.

Lilly and **Boehringer Ingelheim GMBH**'s *Basaglar* (insulin glargine), the first follow-on insulin product approved in the US, received three years of exclusivity when it was approved in December 2015. The Basaglar 505(b)(2) NDA referenced Sanofi's long-acting insulin *Lantus*, and its exclusivity expires in December 2018. *(Also see "FDA Makes It Official With Basaglar Approval For Diabetes" - Pink Sheet, 16 Dec, 2015.)*

Sanofi confirmed that it stands to lose almost nine months of Hatch-Waxman exclusivity because the transition date of March 23, 2020 will pass before Admelog's exclusivity period expires in December 2020.

> "Admelog will offer a more affordable option for those who require control of their blood sugar levels at mealtime." – Sanofi's Oelrich

FDA's draft guidance drew widespread criticism from the pharmaceutical industry, with comments asserting the agency's proposed interpretation of the transition provisions would create a "dead zone" for new applications potentially lasting several years. In addition, the loss of exclusivity that some NDA holders would experience amounts to a violation of the Fifth Amendment's Takings Clause, industry commenters said. *(Also see "FDA Biologic Transition Plan Creates 'Dead Zone' For Applications, Sponsors Fear" - Pink Sheet, 23 May, 2016.)*

The impending regulatory transition may have some insulin product sponsors rethinking their pipelines and development timelines given the risk of non-approval of pending applications by March 23, 2020 and the prospect of lost exclusivity for recently approved applications. *(Also see "Insulin Exclusivity: How Big Will The Fight Be?" - Pink Sheet, 21 Mar, 2016.)*

Further clarity on how FDA intends to implement the transition provisions has not been forthcoming since the draft guidance's release despite the concerns raised by industry and other stakeholders, including payers.

A recent **Express Scripts Holding Co.** blog post focused on promoting biosimilar competition said the March 2020 transition adds "complexity" to prospects for competition from lower-cost insulins, particularly since applications pending as of March 23, 2020 would need to be resubmitted as BLAs which, when approved, carry the prospect of 12 years of exclusivity. *(Also see "Insulin Market Competition: Payers Watching FDA 'Transition' Policy" - Pink Sheet, 6 Jul, 2017.)*

## CURRENTLY, NO LEGAL HURDLES TO LAUNCH

Given that insulin products have been the focus of highly publicized price increases in recent years, it is not surprising that FDA Commissioner Scott Gottlieb used the Admelog approval to highlight the agency's goals of promoting competition and lowering drug costs.

"One of my key policy efforts is increasing competition in the market for prescription drugs and helping facilitate the entry of lower-cost alternatives. This is particularly important for drugs like insulin that are taken by millions of Americans every day for a patient's lifetime to manage a chronic disease," Gottlieb said. "In the coming months, we'll be taking additional policy steps to help to make sure patients continue to benefit from improved access to lower cost, safe and effective alternatives to brand name drugs approved through the agency's abbreviated pathways."

Sanofi said it would provide details about Admelog's price when the product is launched in early 2018. However, the company's press release announcing the approval suggests it will come to market with a price below that of Humalog.

"Complementing our existing insulin portfolio, Admelog will offer a more affordable option for those who require control of their blood sugar levels at mealtime," said Stefan Oelrich, executive vice president and head of global diabetes and cardiovascular at Sanofi.

At this time, there appear to be no legal hurdles standing in the way of Admelog's market entry.

Admelog received tentative approval on Sept. 1, 2017. However, the agency could not grant final approval until after expiration of the 45-day period for Lilly to file suit in response to Sanofi's Paragraph IV certification. Sanofi said Lilly did not file suit within the 45-day period and there is no pending litigation with the company.

*Published online December 11, 2017*

# China Approves Lundbeck Antidepressant In Year-End Dash

**BRIAN YANG** brian.yang@informa.com

**Lundbeck Inc.**'s antidepressant *Brintellix* (vortioxetine) has become the latest new drug approved by China FDA.

The approval for the treatment for severe depression is significant with China, which is increasingly aware of the disease burden of mental health conditions, starting to introduce more novel therapies to the market.

Brintellix is approved by China FDA for major depression disorder, a condition that is largely underdiagnosed and untreated in China, said the Danish drug maker.

There are an estimated 40m people suffering from depression in China, and increasing depression cases have caught the attention of the World Health Organization. The WHO estimates that 54m people in China have depression symptoms; the annual disease burden is estimated $7.8bn in China according to the WHO.

The huge disease burden aside, China has a low diagnosis and treatment rate for depression, because fewer patients actively seek medical help due to the stigma associated with mental health conditions.

The Chinese government has now moved to address the issue, approving novel antidepressant to provide more treatment options.

"The unmet medical needs remain huge and we are proud to be able to provide an innovative and effective treatment option for these patients", said Jacob Tolstrup, Lundbeck Executive VP, Commercial Operations, in a statement.

The company plans to launch the drug in the second quarter of 2018. The product, branded as *Trintellix* in the US and partnered with **Takeda Pharmaceutical Co. Ltd.** has had strong uptake in other regions. *(Also see "Takeda's Deal Flurry Set To Wane" - Scrip, 2 Nov, 2017.)(Also see "Lundbeck 2Q: Raised Revenues But Rocky Route Ahead" - Scrip, 10 Aug, 2017.)*

## CNS MARKET EXPANSION

China's antidepressants market has grown rapidly, with an annual growth of 19% from 2010-2016, making China the world's fifth largest market for such treatment and accounting for 5% of the total market share.

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> Through 2017, China FDA has notably accelerated its new drug approvals, in a bid to prune its approval backlog and start reviews on a rolling basis.

Physician education is likely the center of focus in China as Lundbeck prepares for a market launch of Brintellix. China has an acute need for psychiatrists; there are average 1.7 mental health specialists for 100,000 people, compared to 12 in the US.

Market access will also be critical as there is no reimbursement coverage for a new product upon its approval in China.

"China is our second biggest market and we see a lot of further potential here, so we are investing significantly in making the most of the opportunities presented by these recent approvals." noted Tolstrup.

Lundbeck already markets antidepressants *Cipramil* (citalopram) and Deanxit (flupentixol/melitracen) in China, and *Ebixa* (memantine) for Alzheimer's diseases and *Azilect* (rasagiline) in the country. Since 2010, the Danish drug maker has decided to take a direct selling role by revising the terms with **Johnson & Johnson** to co-market its top-selling *Lexapro* (escitalopram) in China.

Like Azilect, Brintellix will be marketed by Lundbeck on it own, said the company. It is investing heavily in China to expand its local sales force and become a stand-alone company complete with manufacturing and commercial operations.

## MORE CFDA APPROVALS TO COME?

Through 2017, China FDA has notably accelerated its new drug approvals, in a bid to prune its approval backlog and start reviews on a rolling basis.

The agency recently approved a generic to Celgene Corp's *Revlimid* (lenalidomide) from domestic drug maker Beijing Double Crane Pharma, a subsidiary of China Resources Group. The annual sales of the myeloma drug in China was CNY442.5m ($68m) in 2016.

The CFDA recently held expert committee meetings for several new drugs pending approvals, indicating more approvals could be on the way.

One of them is benvitimod, a novel topical treatment for psoriasis that upon approval will become one of few "made in China" innovative new drugs.

Other novel drugs discussed during the expert committee meeting held on Nov. 15 are CephalonInc.'s anticancer *Treanda* (bendamustine), and a domestic generic to **Boehringer Ingelheim GMBH**'s *Atrovent* (ipratropium) inhaler.

Although the agency doesn't necessarily follow the expert committee's conclusions, it generally approves products with positive results from the meetings.

*From the editors of PharmAsia News.*
*Published online December 11, 2017*

# UK's NICE Aims To Knock Firms' Health Economic Models Into Shape

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The National Institute for Health and Care Excellence in the UK has launched a new service for pharmaceutical, medical device and diagnostics companies wanting to ensure that their health economic models are as free of flaws and errors as possible before they make submissions to HTA bodies and payers.

Models submitted for the PRIMA (Preliminary Independent Model Advice) service will undergo a "systematic inspection by a team with years of experience in model development, critique and validation," according to NICE. The team will offer "expert advice on the model structure, data entry and transformations, computations, coding, usability and transparency."

Companies can expect to pay upwards of £15,000 for a "standard" eight-week project, for which they will receive advice on how to improve their model, a completed PRIMA checklist, and an executable copy of the model with proposed changes or corrections.

"PRIMA will enable healthcare companies to health-check their economic models before they submit them as part of the formal evaluation process," said Leeza Osipenska, head of scientific advice at NICE. "This can help them prepare for a dialogue with health technology assessment organisations and payers, better demonstrate the value of their products and, potentially, speed up patient access."

A spokesman for the institute said stakeholders had already shown "encouraging" interest in PRIMA. "We have completed a successful pilot with one pharma company and have a number of projects in the pipeline," he said.

PRIMA was developed in response to recommendations in the Macpherson report on the quality assurance of analytical models that inform government policy. "The introduction of this service was also driven by discussions with multiple stakeholders within NICE, academia and the industry," the NICE spokesman told the *Pink Sheet*.

The institute noted that healthcare organizations were increasingly reliant on the output of economic models to support their decision-making processes, but that the value of these tools depended on their credibility. "Errors in the models can lead to flawed decisions which can be costly for the company, healthcare providers and ultimately patients. Model review is therefore a critical part of the development process as it helps to build decision-maker confidence in the model and its output."

The errors identified in economic models submitted to NICE were "many fold," the spokesman said. "They can range from flaws in the model structure to technical errors such as computational errors, inaccurate data entry and basic programming errors." Although some errors may be minor, "the NICE Technology Appraisal committee often lose confidence in the integrity of the model if many of these have been identified by the independent evidence review group."

NICE already provides advice on the design and structure of economic models at the conceptual stage, but it says that PRIMA offers "an advanced level of service via an external peer review of models that have been implemented in Excel or other specialist modelling software." A detailed report of the review findings will be provided, together with recommendations on any enhancements that could be made to the model.

The HTA body said the new service was likely to be particularly valuable for companies with limited resources, those that have limited experience in modeling, or that have commissioned a model from a third party. "PRIMA would also be recommended if your model represents a high-risk to the business should significant errors be identified by the decision-maker."

It will be available for a wide range of economic models, including those for cost effectiveness analysis, cost consequence analysis, cost minimization analysis, and budget model analysis. Cost-utility models developed especially for a NICE Technology Appraisal will be dealt with on a case-by-case basis. PRIMA may be considered if the model is still under development at the time of the request and the NICE scoping process has not begun.

Models developed for public health interventions, vaccines, and screening technologies can also be considered for PRIMA, as can models for settings and markets outside the National Health Service.

> "Model review is a critical part of the development process as it helps to build decision-maker confidence in the model and its output" – NICE

### COSTS AND DELIVERY TIMES

Noting that it operates on cost-recovery basis, NICE said that the price for a PRIMA review would vary depending on the type of model, its complexity, and the delivery timelines. "An indicative price range for a standard project will be in the region of £15K". The standard delivery time is expected to be around eight working weeks from receipt of the model, although there will be some flexibility to extend it to a maximum of 12 working weeks for complex or *de novo* models.

At the end of the process, the company can request a meeting with the scientific advice department to "clarify any of the key findings in the PRIMA report," NICE added.

Moves are separately under way to implement new methodology to overcomes the perceived weaknesses of currently used economic models. The aim of the Advance Value Framework, developed at the London School of Economics, is to bring more structure and transparency to healthcare decision-making. *(Also see "New HTA Methodology Could Solve Value Conundrum" - Pink Sheet, 22 Sep, 2017.)*

*From the editors of Scrip Regulatory Affairs. Published online December 12, 2017*



# Nonprofit Pharma Targets Making Naloxone Available OTC, Trimming Price

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Harm Reduction Therapeutics Inc. is taking a nonprofit approach to a naloxone OTC switch with a goal of offering it in "every drug store in America" to help prevent opioid-related deaths, says founder and CEO Michael Hufford.

Hufford said the Pittsburgh firm seeks to raise $10m funding to conduct research for an OTC switch application and eventually launch a naloxone product at a low cost with broad availability in some 110,000 retail locations, including 35,000 drug stores as well as gas stations and convenience stores. It also seeks to make the drug widely available to first responders including emergency medical technicians, law enforcement officers and firefighters. Harm Reduction Therapeutics is registered as a tax exempt nonprofit under section 501(c)(3) of the US tax code.

Naloxone is an opioid antagonist indicated for complete or partial reversal of opioid overdose, including respiratory depression. An OTC version would be an intranasal product, the format emergency services personnel prefer to use for opioid overdoses, the cause of 100 deaths in the US per day, Hufford said in an interview.

"I've been doing drug development for 20 years and fundamentally, people's lives are being lost because of a combination of inadequate access and excessive cost" for naloxone, said Hufford, who has co-founded multiple pharma, medical device and mobile health companies, led pharmaceutical development teams through FDA approvals and assisted in Rx-to-OTC switches.

**ANALYZE**

Visit our website at **http://bit.ly/2zcJPIJ** for an overview of naloxone standing order policies and availability without prescription in individual states.

Multiple injectable naloxone generics are available by prescription in the US for use by medical professionals and emergency personnel; two other Rx products in some states are also being made available to consumers: the *Evzio* auto-injector currently marketed by **kaleo Inc.** and **Adapt Pharma Ltd.**'s *Narcan* nasal spray.

## RESPONSE TO FDA PUSH

Harm Reduction Therapies targeted a naloxone OTC switch after FDA Center for Drug Evaluation and Research officials said at a May 2017 consumer health regulatory conference that the agency had funded labeling studies about OTC use, assessing whether pictograms could show "how to safely use naloxone, including when it is appropriate to purchase it and how to use it in an emergency." Division of Nonprescription Drug Products Director Theresa Michele said the research could spur industry interest in resolving unmet public health need and encouraged manufacturers to correspond with the agency regarding potential switch applications. *(Also see "FDA's OTC Naloxone Study Is A Starting Point For Other Switches, Not A Roadmap" - Pink Sheet, 16 May, 2017.)*

Hufford said FDA's effort to prompt switch applications is "remarkable" and "unprecedented" and struck a chord with him.

"As we started talking about it and looking into it, we got more and more frustrated with the status quo that someone needed to do something about it and that someone should be us."

*Michael Hufford: "people's lives are being lost because of a combination of inadequate access and excessive cost" of naloxone.*

The ingredient originally was approved by FDA in 1971 and went off patent in 1985. *(Also see "Amphastar's Naloxone Nasal Spray Delayed; User Human Factors Study Among FDA Concerns" - Pink Sheet, 21 Feb, 2017.)*

In October, President Trump declared the epidemic of people abusing opioid drugs prescribed for pain or using heroin instead of legal substances a national public health emergency and directed all executive agencies to use "every appropriate emergency authority" to stem the crisis. *(Also see "Declaring Opioid Emergency, Trump Touts FDA Actions, NIH-Industry Partnerships" - Pink Sheet, 26 Oct, 2017.)*

## NALOXONE PRICE UP, HEROIN DOWN

Hufford says he is "sickened" that the opioid abuse crisis has spiked naloxone prices. He noted in a recent blog on the firm's website that a nasal spray or auto-injector for use by nonmedical personnel costs $110 and $4,000 as the prices have increased 95% to 500% over the past few years.

Conversely, as naloxone's cost has increased and its availability remains largely unchanged, the cost of heroin has dropped amid growing availability. "What's happened to heroin versus naloxone, they are tragic mirror images of each other," he said.

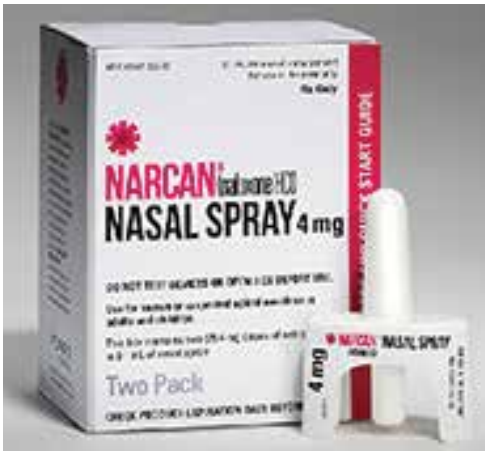
Some states have made Evzio and Narcan available nonprescription from pharmacies, or through pharmacists' prescriptions. In addition to local pharmacies, national drug chains are offering less stringent access to the products where allowed.

But pharmacy sales are "completely insufficient to address the epidemic," Hufford said. The drug still is not inexpensive – $110 for a single nasal spray in the Pittsburgh area, he said.

Access to naloxone still is limited in behind-the-counter distribution because "you still have to interact with the pharmacist, you still have to know what it is in the first place and you are left paying retail or if you have insurance, the co-pay," he said.

Additionally, with the drug needed in emergencies, broader access in venues such as service stations and convenience stores would make it easier to obtain than from a pharmacist.

"Statistically, the most likely person to be present at an overdose is another opioid user, and they may be hesitant to interact with a pharmacist in that situation. So you want them to have it in case they need it to rescue a friend or family member," Hufford said.




*Adapt Pharma's Narcan nasal spray, above, and the Evzio auto-injector marketed by kaleo, below, are deemed Rx by FDA but are available nonprescription from pharmacists in some states.*

> "My goal, to the extent to which we are successfully fundraising, it would be possible to actually sell [the OTC drug] into the retail supply chain at or below cost."
> – CEO Hufford

Hufford said Harm Reduction Therapeutics plans to offer OTC naloxone at a price that will cover manufacturing costs, "functionally at breakeven."

"My goal, to the extent to which we are successfully fundraising, it would be possible to actually sell [the OTC drug] into the retail supply chain at or below cost. The extent to which you have already covered your cost and raise money above that, you would actually use some of that money to offset manufacturing cost."

A nonprofit pharma firm is "an oxymoron in lay people's minds, and the antithesis of how they think of the pharmaceutical industry," Hufford said. Consumers view firms as driven by profit even though drug research and development is costly, he said.

"This is a small opportunity to rehabilitate our image and renew that social contract that when things go off patent and are available in generic form and are life-saving, we have a responsibility to make sure we are fixing the problems of cost and access."

## PUBLIC AWARENESS KEY

A naloxone OTC switch's success will be only as good as consumers' awareness it's available. Harm Reduction Therapeutics is in talks with a group about a public education campaign to inform consumers in much the same way other OTC switch ad campaigns do.

Hufford said he "would love to" have support from the Consumer Healthcare Products Association trade group "We have had some informal communication with folks there to let them know we are doing this, but I haven't asked for support at this point. So, when the time is right we would absolutely reach out to CHPA to make use of their tremendous public education networks and capabilities."

CHPA has conducted campaigns to educate consumers on OTC use and disposal and has ongoing work with several counties in the US on proper disposal to counter the momentum from local governments and one state to require the drug industry to pay for takeback programs. *(Also see "CHPA Optimistic Voluntary Drug Takeback Efforts Will Stall Spread Of Mandates" - Pink Sheet, 6 Jan, 2017.)*

*From the editors of the Tan Sheet. Published online December 12, 2017*

# EU Regulators Urge Pharma To Share Their Brexit Plans

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The veterinary medicines sector is "behaving more pragmatically" than the human medicines sector, though the two sides "can learn from each other." – Hugo Hurts

For medicines evaluated through the EU's decentralized procedure that may be affected by Brexit, the veterinary medicines sector seems to be leading the way when it comes to preparing for the expected extra workload and establishing "best practices", while the human medicines sector is yet to catch up.

Veterinary medicines regulators have already identified that most marketing authorization holders (MAHs) that currently have the UK as the reference member state (RMS) for their medicines evaluated through the decentralized procedure (DCP) or mutual recognition procedure (MRP) are planning to shift the RMS for their products to Ireland and France, if need be.

Ireland and France "really popped out" in a survey undertaken by the EU's Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary (CMDv), said Hugo Hurts, executive director of the Dutch medicines agency, the MEB, at a conference organized jointly by the EU Heads of Medicines Agencies (HMA) and The Organisation for Professionals in Regulatory Affairs (TOPRA) in Tallinn (Estonia) on Dec. 1.

"We regulators want to know what you are going to do [when the UK leaves the EU]," Hurts told pharmaceutical company representatives at the conference, which focused on how to prepare for Brexit. "You may need to know what we can offer [drug companies in terms of procedural help]. Asking each other these questions "will help," he said.

Hurts described the CMDv's survey as an example of a "best practice" initiative. The CMDv had simply counted all the EU veterinary medicines that had the UK as the RMS, and asked to which EU countries did companies intend to transfer their MRP/DCP products in light of Brexit. The survey included 80 products and had an 80% response rate. "From these answers, one could quickly derive that 80% of the firms already knew where they would like to transfer their products in the post-Brexit era," he said.

To the CMDv, it is now clear that Ireland and France will become the RMS for a large majority of the 80 products. With this information in hand, "we can start preparing" and decide on whether Ireland and France will be able "to cope" with this or whether the HMA should make other arrangements "to get it all done. It is important to know these things," he said.

Hurts acknowledged that things were "more difficult" for the human medicines sector because much more products and procedures are involved. "I don't even know if we have a list of all [UK-affected] MAHs readily available, and whether it is possible to set up a survey like this… But it's important to have this information," he said.

He explained that the CMDh (Coordination Group for Mutual Recognition and Decentralised Procedures – Human) is also making attempts to interact with the industry to get information on crucial Brexit-related issues, and has already held two meetings. Another meeting is scheduled in Feb. 2018. Hurts' personal impression is that the veterinary medicines sector is "behaving more pragmatically" than the human medicines sector, though he adds the two sides "can learn from each other".

Beata Stepniewska, of EU generics industry association Medicines for Europe, said the trade body was encouraging its member companies "to communicate their Brexit plans to all national authorities as soon as possible, and I hope that they will take this advice seriously".

## DEDICATED UK TASK FORCE TO CLOSE OPEN PROCEDURES

As the RMS cannot be changed if there is a pending procedure (e.g., a renewal or variation) in relation to a product, Hurts said that the UK has recently set up a dedicated task force to close all "currently open" renewal procedures before the end of this year.

Stepniewska, who is deputy director general and head of regulatory affairs at Medicines for Europe, said this was a welcome step as companies had identified the issue of open procedures as the "main barrier" to getting started on the process of

A new Brexit task force has now been set up by the HMA to coordinate the efforts of various working groups involved in dealing with Brexit-related changes to decentralized products.

changing their RMS. By the middle of this year, there were about 700 open UK procedures in relation to MRP/DCP products.

Medicines for Europe has been advocating for flexibility on this issue and wants companies to be allowed to apply for the RMS to be changed even if there is an ongoing variation or an ongoing renewal. "At the moment, our proposal has not drawn big support. If these pending procedures are not closed by early next year, we will have to think realistically about this [proposed] option," Stepniewska said.

Hurts emphasized the need to find pragmatic solutions. He pointed out that the CMDh already offers a shortened procedure for changing the RMS.

## NEW HMA BREXIT TASK FORCE

A new Brexit task force has now been set up by the HMA to coordinate the efforts of the CMDh, CMDv, and the other working groups involved in dealing with Brexit-related changes to decentralized products.

Hurts is chairing the new task force. Thomas Heberer, from Germany's veterinary medicines agency BVL, is the co-chair. The HMA Brexit task force was established two weeks ago, and reported to the HMA plenary for the first time last week.

The initial plan was to have a small, operational Brexit coordination group, but the subject drew huge interest from most members of the HMA plenary, Hurts remarked. *(Also see "Brexit Won't Alter EU Agency Heads' Ambitious Work Plan – For Now" - Pink Sheet, 4 Oct, 2017.)*

The task force currently has 18 heads of medicines agencies as its members as well as the chairs of CMDh and CMDv, who will continue doing most of the work. "I guess, we are going to add representatives of other [HMA] groups as well once we start talking about inspections, clinical trials and other subjects. So the group would become larger," Hurts said.

The task force, which has agreed to meet every two months, will:

- **Prepare the EU medicines network for the worst-case Brexit-scenario with a focus on decentralized activities and practical issues** – Hurts thinks it is necessary to prepare for the worst-case scenario despite several industry members questioning such an approach. "We can't afford to wait" till the end "only to find out that nothing has been negotiated," he said. He warned companies: "If you wait a long time…and only start acting by the end of 2018, you will surely run into problems."
- **Build oversight to ensure regulatory continuity of the network** – Hurts believes that building oversight will be a difficult task. While the European Medicines Agency is looking at centrally authorized products, and the HMA Brexit task force will focus on decentralized products, he thinks "it will be a challenge to bring these together". This is because at national agencies, the staff members "are never only doing centralized procedures or only doing decentralized procedures –they mix it up all the time. So you can never think that 'OK, we have enough capacity to cover the centralized procedure, and lets focus on decentralized procedure'…We have to combine it – so oversight is very essential."
- **Work in close cooperation with the CMDh, CMDv and other HMA working groups and organizations, including the EMA, on Brexit-related issues, and build upon existing efforts.**
- **Coordinate Brexit queries and the coordination groups' responses to them** – The aim will be to make clear "not only what we know, but also what we don't know".
- **Identify outstanding issues in Brexit preparations and involve relevant groups and bodies** – The CMDh and CMDv have already identified two issues that cannot be handled at their level. These relate to ensuring adequate capacity to take over procedures being led by the UK, and handling of fee-related problems at national agencies. "It's a complicated one but that's our responsibility," Hurts said.
- **Consider industry's preparedness in its recommendations and proposed actions** – Hurts believes cooperation between regulators and industry on Brexit is key to preventing problems.

## MAPPING THE NETWORK'S CAPACITY: NEW EMA-HMA SURVEY

Hurts explained that an initial survey undertaken by the EMA in June/July this year to map the capacity of the medicines network did not yield clear answers. As a result, the EMA is planning to launch another survey on this topic early next year.

In the first survey, the EMA had asked each national competent authority what preparations they were making for Brexit, which issues they planned to address, whether they planned to expand their capacity overall or in a specific therapeutic specialty.

While the survey drew an "interesting level of response," Hurts said there is still misinformation and "not every answer given seems to be… reliable." The EMA and HMA will work together to set up the next survey, which would hopefully result in a "better understanding of the capacity that the network can offer to keep things going and guarantee continuity," he added.

*From the editors of Scrip Regulatory Affairs. Published online December 8, 2017*

# The Impact Of Brexit – Delays, Safety Impacts And Costs Across Four Scenarios

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If Brexit results in the UK and the EU no longer cooperating in medicines and public as they do today, there could be delays of up to five months in the sharing of new drug safety information, several months' delay in the launch of new drugs, and a higher risk of medicines shortages because of new administrative requirements, customs delays and tariff barriers.

Those are among the conclusions of a report by the UK Office of Health Economics that has just been published by the BioIndustry Association and the Association of the British Pharmaceutical Industry. Its conclusions will be used to urge the UK government and EU Brexit negotiators to safeguard public health by making the regulation and supply of medicines "the first priority" in phase two of the Brexit talks, the associations said.

Much has already been said about the potential impact on life sciences and healthcare of the UK leaving the EU at the end of March 2019. However, this report goes further and looks at the likely consequences of legal and regulatory changes in each of four scenarios involving different combinations of trade and regulatory agreements, from continuing full UK/EU cooperation on trade and public health all the way to no cooperation at all.

Industry wants close cooperation between the UK and the EU post Brexit and is seeking a transition period that would provide for continued EU-UK partnership on medicines regulation and supply while a future cooperation agreement is negotiated.

The four scenarios are as follows:

- **Scenario 1:** The UK Medicines and Healthcare products Regulatory Authority (MHRA) remains fully involved in EU27/European Economic Area public health activities, and the UK negotiates free trade agreements (FTAs) with the EU.
- **Scenario 2:** The MHRA implements a standalone regulatory system and negotiates agreements with the EU covering inspections of quality and manufacturing processes (but not batch release), and the UK negotiates FTAs with the EU.
- **Scenario 3:** As per scenario 2, but with trade cooperation regulated by World Trade Organization "most favored nation" (MFN) agreements.
- **Scenario 4:** No public health cooperation between the MHRA and the EU27/EEA, and trade cooperation is regulated by WTO MFN agreements.

In scenario 1, the presumption is that things would stay pretty much as they are now. Matters take a sharp turn, however, when the other scenarios come into play.

For example, the report says that where centralized marketing authorizations are concerned, under scenario 2 a transposition into UK law will have to be performed for the 978 medicinal products that have been approved between 1995 and July 2017. The effect for the EU27/EEA is that the MA holder will have to be transferred from a UK holder to one in the EU/EEA for more than a third of these products (361; 37%), the report says.

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> "The median lag of submission could be 2-3 months based on existing submission delays in third countries" – OHE report

For products approved after Brexit, scenario 2 could lead to a lack of submissions and delays in MAA submissions compared with scenario 1. "The median lag of submission could be 2-3 months (based on existing submission delays in third countries for centrally authorised products containing a new active substance)."

## SAFETY ISSUES

In scenarios 2-4, delays of one to two months would be seen in the detection of new safety signals in the UK and the EU27/EEA, because of the loss of connection between the MHRA and the EU IT public health network, including the EudraVigilance database. The management of new signals could be delayed by two to five months because of the lack of direct communications, the report says.

For post-authorization studies in those three scenarios, the report says that the "UK and the EU27/EEA face the loss of expertise in their respective regulatory networks and a loss of resources for the conduct of PASS [post-authorization safety

studies]." It notes that the UK contains the highest number of centers in Europe for the conduct of pharmaco-epidemiology studies (35, or 22%). The UK also conducts the highest number of PASS (164, or 50%).

### PRODUCT SHORTAGES

In scenario 2, some drugs could be in short supply (in the UK for the products manufactured in the EU27/EEA and in the EU27/EEA for the products manufactured in the UK) because of the lack of mutual recognition of batch release between the UK and the EU. Scenario 3 would also see the disappearance of parallel trade in medicines between the UK and the EU.

"Our analysis confirms the UK as a major importer and exporter of pharmaceutical products," the report's authors say. The UK imports around 54% of its pharmaceuticals from Germany, the Netherlands and Belgium and exports 48% of its medicines to Germany, the Netherlands and France. "Customs delays and/or tariff measures that complicate the movement of this quantity of products between the UK and the EU27/EEA could have substantial implications for public health in both jurisdictions."

The report also foresees risks relating to delays in the supply of medicines from outside the EU, the BIA and ABPI say. They note that the UK has the highest number of sites certified to import pharmaceuticals from "third countries", ahead of Germany, and that currently, products from third countries certified at sites in the UK "can be readily dispatched to the EU27/EEA through the single market and customs union."

### COSTS TO COMPANIES

The report gives some figures for the estimated financial impact on companies for the different areas in each of the scenarios. For example, the estimated cost of Brexit in year one for a UK-based company is assumed to be £39.1m under Scenario 2, £66.6m under Scenario 3, and £80m under Scenario 4.

"These costs could distort incentives for manufactures by reducing the attractiveness of manufacturing and investing in the UK. In addition, our analysis has assumed that these costs will accrue from March 2019. In reality, in the absence of a clear signal from Government about the exact nature of any transition period post March 2019, companies may be forced to plan for the 'worst case' (i.e., Scenario 4) and some of the costs that we have identified may be incurred in advance of this deadline."

BIA CEO Steve Bates said that the complex issues surrounding medicines regulation and supply chain "need to be front and centre in the second phase of talks and industry needs a realistic transition period to ensure that the supply of lifesaving and life extending medicines to patients in the UK and across Europe is not affected." Bates was among those giving evidence to a Dec. 12 hearing of the House of Commons' health select committee on "Brexit: the regulation of medicines, medical devices and substances of human origin."

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



# How Biocon Site Prevented FDA 'OAI' Finding From Derailing Biosimilars

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US FDA had considered issuing an "official action indicated," or OAI, classification for a **Biocon Ltd.** facility in Bangalore, India, but after the firm addressed key issues raised during a May 25 through June 3 inspection, the agency instead closed out the inspection in November as "voluntary action indicated," or VAI.

If the agency had decided on an OAI classification, it could have potentially delayed approval of Mylan's biosimilar Herceptin (*trastuzumab*) and Neulasta (*pegfilgrastim*), which Biocon, India's largest biopharmaceutical company, is expected to manufacture at the site.

The VAI classification Biocon announced Nov. 20 lists compliance issues the company still must address at its Bangalore site (Plot 2-4, Phase IV, Bommasandra Ind.), but does not block any approvals.

FDA's lead investigator and a branch chief in the agency's Office of Regulatory Affairs initially proposed an OAI classification over the summer, an establishment inspection report FDA provided the Pink Sheet shows.

ORA supervisors and compliance officials in FDA's Center for Drug Evaluation and Research may have overruled them, or they may have agreed, only to later reclassify the site as VAI after the company addressed key issues. The agency does not disclose the 481(e) forms that show how sites are classified, and typically only releases EIRs after any OAI classifications are downgraded.

Asked whether the FDA had reclassified the inspection at the Bangalore unit as VAI from OAI, Biocon told the Pink Sheet, "As previously stated, we have implemented the CAPAs [corrective and preventive actions] requested by FDA and received the EIR and VAI rating. We have no other information on the classification of the inspection."

An OAI inspection classification in general results when signifi-

cant objectionable conditions or practices are found and regulatory action is warranted to address the deviations.

EIRs are generally issued when no enforcement action is contemplated, or after enforcement action is concluded. An EIR typically includes, among other details, the investigator's narrative report and any refusals, voluntary corrections, or promises made by the firm's management.

Significantly, on Nov. 20, Biocon said that the FDA had issued an EIR in relation to the May 25 through June 3 inspection of the aseptic drug product facility in Bangalore.

"The FDA has classified the outcome of this inspection as VAI (voluntary action indicated) and the EIR states that the inspection is closed," the Bengaluru-based company said at the time. A VAI inspection classification usually suggests that objectionable conditions or practices were found that do not meet the threshold of regulatory significance. However, inspections classified with VAI violations are typically more technical violations of the Food, Drug and Cosmetic Act's current good manufacturing practice (cGMP) provisions.

Biocon also did not provide any specific comments on whether the FDA Complete Response Letter for partner **Mylan NV**´s Biologics License Application (BLA) for MYL-1401H, a proposed biosimilar pegfilgrastim, was a result of a possible OAI at the Bangalore site. The Indian company only reiterated details in its Oct. 10 statement pertaining to the CRL; it said that the CRL relates to the pending update of the BLA with certain chemistry, manufacturing and controls data from facility requalification activities conducted after recent plant modifications. *(Also see "Keeping Track: FDA Hands Out Complete Responses, Expedited Pathway Designations" - Pink Sheet, 15 Oct, 2017.)*

"The CRL did not raise any questions on biosimilarity, pharmacokinetic/pharmacodynamic data, clinical data or immunogenicity," it said at the time. Biocon also clarified that commercial launch timelines of biosimilar pegfilgrastim in the US are unlikely to be impacted by the CRL. More recently, FDA Dec. 1 approved the first biosimilar to **Genentech Inc.** 's Herceptin (trastuzumab) from Mylan and Biocon. The Indian company, though, did not immediately clarify why the label for biosimilar trastuzumab suggests that the product will be manufactured by Mylan GmbH, Zurich.

## EIR DETAILS

Meanwhile, the EIR encompasses, among other details, specifics of the 10-item FDA 483, following the audit at the Bommasandra site in Bangalore done between May 25 and June 3. A Form 483 is a notice of the FDA's inspectional observations that lists deficiencies in the quality system.

One key observation was that Biocon had inadequately investigated particles seen since August 2015 during stability studies of certain sterile injectables. The firm resumed shipments to Uruguay, Russia and the Dominican Republic in April 2016 after determining the particles were "not a big deal," as it was apparently "seen in the innovator samples", the EIR said. The Biocon management also said that they continued to look into the particles as part of continuous improvement. Asked if the firm had notified Uruguay, which was getting the majority of the product, about the particles, management said Uruguay's supply agreement did not require it.

Some of the key observations include that the firm does not perform risk assessments on how the product on the market could be affected when they determine inadequate practices/procedures were being used. It also specified that aseptic personnel are not tracked and there are no requirements for qualifying personnel who participate in a media fill.

"Media fills do not represent actual run times," the observations listed in the EIR note.

Other observations pertain to how all interventions were not being documented during filling and that inadequate aseptic behavior was observed during aseptic filling operations.

Biocon had earlier indicated that the FDA visit in May/June was a part of the regular periodic audit for a small molecule injectable. At the time, Biocon had also suggested that the observations were mostly related to procedural inadequacies stemming from "heightened regulatory expectations", which the company is addressing through its CAPA implementation. *(Also see "Will FDA GMP Observations Stall Biocon's Run?" - Pink Sheet, 7 Aug, 2017.)*

*Published online December 12, 2017*

# FDA Mulls Which EU Inspections To Skip Under EU MRA

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US FDA is studying which inspections it can skip in fiscal year 2018 now that it has recognized the inspectorates of eight European countries under a mutual recognition agreement with the EU, Alonza Cruse, who directs the agency's Office of Pharmaceutical Quality Operations, told a Food and Drug Law Institute meeting in Washington, DC.

FDA said Oct. 31 it would recognize the regulatory authorities of Austria, Croatia, France, Italy, Malta, Spain, Sweden and the UK "as capable of conducting inspections of manufacturing facilities that meet FDA requirements."

But that doesn't mean FDA will rely on those authorities to decide which sites to inspect when.

When the agency ran its site selection model to help it decide which sites to inspect in FY 2018, the model flagged 256 facilities in the eight EU countries that were due for a surveillance inspection, Cruse told the Dec. 6 FDLI meeting.

To see whether some of these inspections can be deferred to domestic inspectorates, FDA is "reaching out to these countries to see if they have recently either conducted an inspection and/or are planning an inspection in this fiscal year," Cruse said.

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In such cases, FDA would consider relying on the domestic inspectorate's inspection reports, at least for surveillance inspections and under certain conditions pre-approval inspections.

Cruse said one of OPQO's headquarters offices has established "the structure that will begin reviewing the reports as they come in." OPQO is part of the Office of Regulatory Affairs, which oversees FDA's field organization.

Reuse of other countries' domestic inspections "to help make determinations about GMP issues before us … will allow our regulatory systems to operate more efficiently," Cruse said.

He stressed that the mutual recognition agreement benefits industry by averting duplicate inspections.

But before that can happen, FDA must decide which inspections to forgo.

As FDA's relationships with EU member state authorities evolve, Cruse told the Pink Sheet it is possible that the agency may rely more on EU inspection priority setting.

## FDA ON TARGET FOR JULY 2019 DEADLINE

Cruse said FDA is slightly ahead of schedule in its assessment of European authorities. The agency plans to complete four assessments by March. Three are underway and the fourth is about to begin, he said.

The agency plans to finish assessing two more countries in June, another six in December and the final eight in July 2019, just in time to meet the mutual recognition agreement's deadline. "By all indications, we will be on target to meet the assessments of all 28 EU member states by July 2019," Cruse said.

*From the editors of the Gold Sheet.*
*Published online December 13, 2017*

# FDA's First 90-Day Letters To Deliver Inspection Outcomes After Jan. 1

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Drug manufacturers that US FDA has inspected since Oct. 1 will know after the New Year whether their facilities pass muster under Generic Drug User Fee Amendments II deadlines.

The agency is issuing these so-called 90-day letters a year earlier than required under the second round of the generic drug user fee amendments, known as GDUFA II, that Congress approved as part of the FDA Reauthorization Act in August.

Generic drug firms had requested the letters as part of GDUFA II negotiations to give them more time to respond if FDA inspections identified major problems at their contract manufacturing organizations. Even though brand firms didn't ask for 90-day letters as part of their user fee negotiations, they will get them too.

> Former FDA official Thomas Cosgrove says the program is a vast improvement in that it specifies much-needed goals for making regulatory decisions following inspections.

FDA officials and legal observers said that a concept of operations (ConOps) agreement between the agency's Office of Regulatory Affairs and its Center for Drug Evaluation and Research, which incorporates user fee commitments under GDUFA II like the 90-day letters, and which complements the agency's program alignment initiative, is a vast improvement.

There was agreement that ConOps standardizes workflows for pre-approval, post-approval surveillance and for-cause inspections in the US and abroad. FDA speakers touted its benefits Dec. 7 at the Food and Drug Law Institute's enforcement conference in Washington.

Under GDUFA II, which went into effect on Oct. 1, FDA has 90 days following a surveillance inspection to make inspection classification decisions. That means that firms will know within 90 days whether their facilities have been classified as no action indicated (NAI) if there are no problems; voluntary action indicated (VAI) if there are minor observations and official action indicated (OAI) if the problems described are so serious that they warrant FDA issuing a warning letter.

The ConOps agreement, released over the summer, spells out how FDA's realigned inspectorate and program offices will work together to accelerate drug manufacturing facility evaluations and inspections in line with generic and brand drug product reviews. *(Also see "FDA Accelerates Inspection Process With New Concept Of Operations" - Pink Sheet, 25 Aug, 2017.)* The new approach also complements the reorganization of FDA's Office of Regulatory Affairs in May, which aligns field staff with CDER and the agency's other centers.

## BETTER THAN CHRISTMAS

Paula Katz, director of manufacturing quality guidance and policy in the CDER Office of Compliance, said that one of the first tangible things the industry will see out of GDUFA II is the 90-day classification letter.

Katz said any surveillance inspection that closed on Oct. 1 or after is covered by the agreement. "That will include the issuance of the 90-day decision letter for cases that my office ultimately determines are OAI classifications. You will see that. Happy New Year for anybody who had an inspection close. This will be on or around New Year's. Sorry to ruin the holiday for some people but that is how it happens. Its's better than Christmas I guess."

A former FDA official agreed that this is a "significant" timeline that will put pressure on inspectors to act quickly in issuing decisions following an inspection.

Thomas Cosgrove, who was deputy director of compliance at CDER until Nov. 30, when he left the agency to rejoin the law firm Covington & Burling as a partner, said that "you will be getting these classifications in 90 days and final means final. What does that mean for people working on these classifications? That means they will be working quickly. I mean they will be cutting to the most important part of the inspection and making a disciplined decision in a short amount of time."

Cosgrove said that the accelerated timeline "raises the possibility that there are going to be more OAIs and more enforcement actions."

## STEADY FLOW TO DELUGE

Cosgove said that the program is a vast improvement over the former program in that it specifies much-needed goals for making regulatory decisions following inspections.

"We went from a phase in FDA history where we had a steady flow of mostly domestic cases and our processes and procedures were able to account for them and we had a relatively quick turnaround. You enter the age of GDUFA and we started doing hundreds of foreign inspections, many of which came out OAI. In the Office of Compliance, we went from a trickle of interesting cases to a deluge of all kinds of cases and that caused our warning letter timeline to become delayed."

Cosgrove said that under the former approach, a classification was not final until the warning letter was issued. Consequently, he said, "you end up in this dilemma where the warning letter is taking longer, therefore the final classification is taking longer. There is a pending enforcement action and there is a reluctance among compliance officers to talk with the company while this is happening and you have a perfect storm of uncertainty and that is what we were hearing about over and over again. Companies were saying we just want to know where we stand."

Cosgrove noted that the 90-day classification letter gives manufacturers, particularly generic manufacturers, a clear idea of the compliance status of their contract manufacturing partners. "In the generic industry … there is more use of CMOs and more complex supply chains and there are sponsors with relatively far flung manufacturing chains and not the kind of knowledge of their contract manufacturers. So they did not know the status of the manufacturing facilities."

Katz said that another benefit is that ConOps improves transparency in describing, through the use of flow charts, which office is responsible for which activity before, during and after an inspection. These flowcharts are available to the public and are in the ConOps agreement.

## PROGRAM 'LONG OVERDUE'

FDA's Alonzo Cruse, who had a lead role in the realignment as it relates to pharmaceutical inspections, said that ConOps was long overdue.

He said that under the old model, "we had compliance officers in CDER and CVM and compliance offices in the field and you would think we are working from two different CFRs. We really had to work together to bring our philosophical and management

and operational approaches in line with one another. The reality is that we are working for the same compliance program but we had somewhat disparate approaches in how we went about it. I am not saying that in a bad way and that one side is as wrong, both sides I think bring in a valuable level of diligence to the work that they do."

Cruse said that the program has been expanded to include more types of inspections since it was first proposed. "When we first started developing this concept in the 2015 timeframe, OPQ [the Office of Pharmaceutical Quality] led this initiative and ORA [the Office of Regulatory Affairs] became more involved in July 2016 and then we first started looking at preapproval and surveillance, that was our initial focus and then it became clear … why are we just limiting it to that? Let's include additional inspectional types and so that is where we began."

### REMOVES GUESSWORK

Alison Fulton, a partner with Sidley Austin, said that clients in her practice "are encouraged" by ConOps. She said that "my clients, which are pharmaceutical companies and makers of dietary supplements, they used to have to wait a long time for decisions to come down and that affected their business and their operations."

She said that the one drawback with the program is that it does now allow for much interaction with FDA inspectors after inspections.

Fulton said that many companies "will want to start remediation immediately after an inspection closes and will want to know how they can adjust course before they get too far down the road."

*From the editors of the Gold Sheet. Published online December 11, 2017*



# FDA's NDA And BLA Approvals: Xepi, Admelog, Ixifi

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

| SPONSOR | PRODUCT | INDICATION | CODE | APPROVAL DATE |
|---|---|---|---|---|
| **New Drugs** | | | | |
| Intersect ENT | *Sinuva* (mometasone furoate) | Corticosteroid-eluting implant to treat nasal polyps in patients age 18 years and older who have had ethmoid sinus surgery. | S, 3 | 12/8/2017 |
| Ferrer | *Xepi* (ozenoxacin) | Cream for the topical | S, 1 | 12/11/2017 |
| Sanofi | *Admelog* (insulin lispro) | Short-acting insulin follow-on product | S, 5 | 12/11/2017 |
| **New Biologics** | | | | |
| Pfizer | *Ixifi* (infliximab-qbtx) | Biosimilar of Janssen's tumor Remicade (infliximab) to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. | | 12/13/2017 |

| KEY TO ABBREVIATIONS | |
|---|---|
| **Review Classifications** | **NDA Submission Classification** |
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# Minimal Residual Disease 'Coming Soon' As An Approval Endpoint, Celgene Says

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**Celgene Corp.** believes minimal residual disease (MRD) may someday be the ticket to approval of its investigational chimeric antigen receptor T-cell (CAR-T) therapy in early lines of multiple myeloma, even though the regulatory path is currently uncertain.

The company's management spoke about the prospects for MRD to serve as a surrogate endpoint supporting approval during a Dec. 10 investor presentation at the American Society of Hematology (ASH) annual meeting.

The issue came up in the context of the company's discussion of impressive Phase I data for bb2121, a CAR-T therapy that targets B cell maturation antigen. The agent is being developed in collaboration with **bluebird bio Inc.**

In the study of heavily pre-treated multiple myeloma patients, 17 out of 18 subjects (94%) treated with bb2121 dosed at 150m, 450m or 800m cells achieved an objective response, with a complete response (CR) rate of 56% (10 out of 18) at data cut-off.

Patients in the study had a median of seven prior lines of therapy and had received at least one autologous stem-cell transplant.

"The data that really surprised all of us when it first came out, we started looking very early for evidence of minimal residual disease using a next-gen sequencing assay that picks up one in 100,000 residual myeloma cells," said Kristen Hege, vice president of translational development for Celgene's hematology/oncology programs. "As early as four weeks, you can see most of these patients were MRD-negative."

In total, nine of 10 patients for whom there were evaluable MRD data were negative, and most patients retained this status with longer-term follow-up. The only one of the 10 patients who did not achieve MRD-negative status did not respond to treatment, Hege said.

Median duration of follow-up in the trial is 40 weeks, and median progression-free survival (PFS) has not been reached. However, PFS rates at six and nine months were 81% and 71%, respectively.


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In a Phase I study of heavily pre-treated myeloma patients, MRD-negative status was reported for 90% of patients with evaluable samples.

"The MRD data, I think, is really unprecedented," Hege said. "Moving forward we plan to collect a lot of MRD data because we think it's going to be very valuable."

## CAN MRD SPEED THE ROUTE TO EARLIER-LINE SETTINGS?

Celgene and bluebird recently initiated a global pivotal trial, KarMMa, a single-arm study that will enroll at least 80 patients who have failed at least three prior regimens, including an immunomodulatory drug, a proteasome inhibitor and an anti-CD-38 agent.

The primary endpoint will be overall response rate, with the aim of supporting accelerated approval in this refractory setting. Key secondary endpoints will be complete response rate and MRD. "We plan to test that using genomic assays, ultrasensitive flow assays and gather that data very frequently over the course of the trial to document the durability of these deep MRD negative responses," Hege said.

The fourth-line myeloma trial will be followed by a Phase III, randomized trial in the third-line setting, where bb2121 will be tested against the combination of Celgene's *Pomalyst* (pomalidomide), **Janssen Biotech Inc.**'s *Darzalex* (daratumumab) and dexamethasone.

PFS will be the primary endpoint, with secondary endpoints including complete response rate, MRD negative rate and survival.

"We of course are also going to explore label expansion opportunities in the second-line setting," Hege said. "And we're looking at our opportunities in first-line myeloma in high-risk patient populations."

Hege's presentation prompted a question as to how long it might take to secure approval for first- or second-line indications and whether using MRD negativity as a surrogate endpoint could speed up the process.

Nadim Ahmed, president of hematology and oncology, said that for bb2121, if a trial took a "broad all-comers approach to the front-line setting, you'd be waiting a long time for those results."

"I think that's where we have to be smart," Ahmed said. "If you think about high-risk disease, that's still an area where we see very, very poor outcomes. You combine that with a potential MRD approach, then I think you can start to develop a very creative approach to kind of get there quicker than you perhaps traditionally would. And we're looking at all of those opportunities."

Complete response "translates into long-term outcomes in myeloma. MRD negativity, we could argue, is a super CR." – Celgene's Backstrom

## WHERE DO THE REGULATORS STAND?

When asked where regulators currently stand on their willingness to engage in discussions about MRD negativity as an endpoint, Chief Medical Officer and Head of Global Regulatory Affairs Jay Backstrom responded, "Stay tuned."

"I think I'm on record of saying it's coming soon, maybe about a year or two ago," Backstrom said. "I can tell you that the academics want it, the data are coming. We know how to get there. And there's a collaborative effort underway now, so coming soon."

"FDA has been on record of giving guidance for how to get there," Backstrom said. "CR translates into long-term outcomes in myeloma. MRD negativity, we could argue, is a super CR really driving it down. And today, you could embed that into a study."

"The real question is whether or not you can get an early approval on the MRD negativity endpoint while you wait for the longer-term outcomes," Backstrom continued. "That's where they haven't established guidance to give us as a surrogate, but I really do think the data are beginning to show the way. And it's just a matter of getting through the regulatory hurdles, but we could run a study today with that embedded. And companies are doing that."

When it comes to the ability of MRD to support approval in multiple myeloma, Ahmed said, " I think somebody just probably has to bite the bullet and do the study, the definitive prospective study, because I think the feel … we're getting from regulators is there's a lot of academic work done in this setting which will help to build the case, but I think probably what they want to see is some sort of prospective-built study to really test that question."

"I think we'll be able to definitely get there, but we're just going to have to show that MRD does pertain to longer-term outcome," Ahmed said.

## FDA NOT YET CONVINCED

FDA has signaled that while it is enthusiastic and supportive of efforts to establish MRD as a surrogate for clinical benefit in hematologic malignancies, it is not yet convinced.

In an editorial published in the January 2017 issue of JAMA Oncology, senior officials in the Office of Hematology and Oncology Products (OHOP) highlighted "lingering questions" about use of MRD as a potential surrogate endpoint. These include the threshold for defining an MRD level that best correlates with clinical benefit, the ability of MRD to predict responses in different lines of treatment and different patient populations, the timing of assessment, and the most appropriate testing methods.

The agency raised similar concerns at a September 2016 stakeholder workshop. However, one agency official also suggested that rigorous MRD data collection in clinical trials would help advance use of the marker for regulatory purposes. *(Also see "Cancer Trial Endpoints: Minimal Residual Disease Eyed As Surrogate" - Pink Sheet, 20 Sep, 2016.)*

Despite FDA's publicly expressed concerns, Celgene President and Chief Operating Officer Scott Smith suggested the atmosphere is ripe for the agency's acceptance of MRD as a surrogate.

More recently, Amy McKee, OHOP's supervisory associate director, told the Friends of Cancer Research annual meeting that the agency does not currently view the data sufficient to support the use of MRD as the basis for an approval. *(Also see "Supplemental Oncology Approvals: 'Reverse Accelerated Approval,' Not Lowering The Bar" - Pink Sheet, 27 Nov, 2017.)*

## 'ERA OF WILLINGNESS' TO DOING THINGS DIFFERENTLY

Despite FDA's publicly expressed concerns, Celgene President and Chief Operating Officer Scott Smith suggested the atmosphere is ripe for the agency's acceptance of MRD as a surrogate.

"I think there's a willingness within the regulatory authorities, particularly the FDA under Scott Gottlieb's leadership right now … to look at different approaches, to think about ways that we can get transformational therapies into patients' hands earlier," Smith said.

FDA is open to reconsidering the need for long trials and whether biomarkers can help get products to market more quickly, he said.

"I think there's a real era of willingness to try and do some different things to be able to answer some of these questions right now," Smith said. "It's let's wait and see. … But I think it feels to me like the discussions are productive and the environment is at least susceptible to that."

BMO Capital Markets analyst Ian Somaiya also found reason to be hopeful that regulatory approval based on MRD negativity isn't such a far-fetched idea.

In a Dec. 11 note, Somaiya said that following several supportive clinical trial presentations at ASH correlating MRD to PFS and overall survival, "plus evidence that new assay technologies are improving sensitivity to levels not previously achieved with near 100% predictive potential, we are inclined to agree with Celgene management, who indicated at their analyst event that approvability on MRD negativity should be 'coming soon.'"

*From the editors of the Gold Sheet.*
*Published online December 13, 2017*

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| Lipocine's oral testosterone undecanoate capsules for testosterone replacement in males for conditions associated with a deficiency or absence of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired) | Bone, Reproductive and Urologic Drugs | Jan. 10 |
| Aradigm Corp.'s ciprofloxacin dispersion for inhalation for treatment of non-cystic fibrosis bronchiectasis patients with chronic lung infections with *Pseudomonas aeruginosa* | Antimicrobial Drugs | Jan. 11 |


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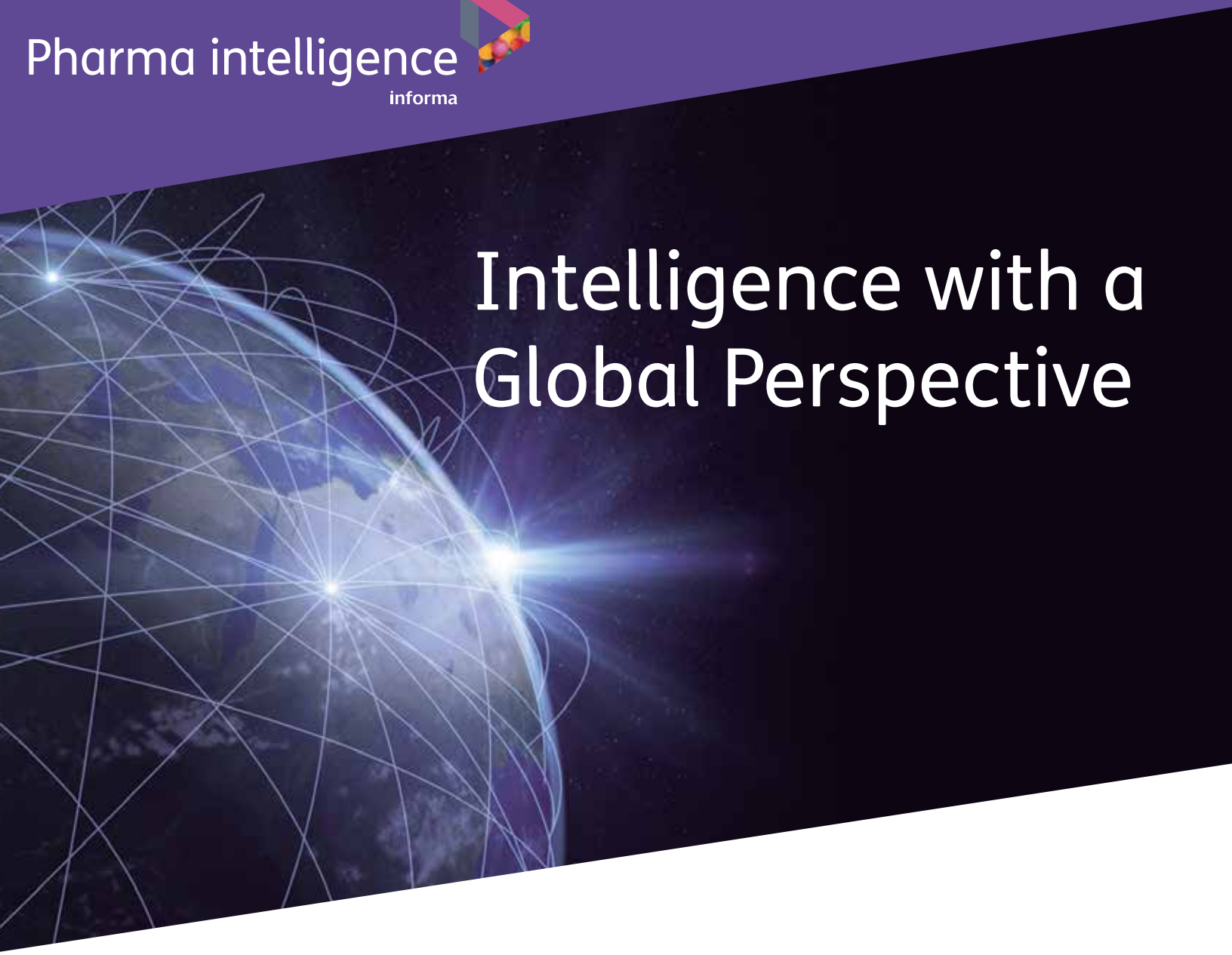

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