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FDA Drug Pricing Policy Offers Short-Term PR Gain, More Long-Term Actual Benefit

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FDA appears poised to more quickly increase generic competition with its expanded ANDA prioritization policy, but stakeholders may be disappointed if they expect any immediate gratification from the changes.

Instead of offering priority only to first generics, the agency now will offer it for generics where there are "fewer than three ANDAs approved for the reference listed drug" and there are no blocking patents or exclusivities, according to an updated Manual of Policies and Procedures (MaPP) document posted June 27.

The change is part of FDA's Drug Competition Action Plan, which is its response to problems with rising drug prices. The agency cannot take price into account when deciding whether to approve a drug, but Commissioner Scott Gottlieb has emphasized that FDA can promote competition. *(Also see "Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff" - Pink Sheet, 16 May, 2017.)*

Keith Flanagan, director of FDA's Office of Generic Drug Policy, said in an interview with the Pink Sheet that the agency wanted to plug a perceived gap. Expanding prioritization is less about the volume of applications that it could help and more about targeting, he said.

After the first filers are approved and blocking patents and exclusivity are removed "we want to keep the pedal to the metal until at least three [have been approved] and that wasn't previously our policy."

Under the old MaPP, subsequent applicants received a standard review unless they qualified under one of the other priority categories.

The new MaPP, which governs internal FDA workings, says that expedited review means that the ANDA will receive "heightened review priority as determined by the [Office of Generic Drugs] Division of Project Management staff." FDA has said that it would try to act on ANDAs with a priority designation before the goal date.

GDUFA II, which is scheduled to launch Oct. 1, promises an eight-month priority review pathway. *(Also see "ANDAs Can Get Priority, Eight-Month Reviews Under User Fee Deal" - Pink Sheet, 24 Sep, 2016.)* The MaPP is expected to guide eligibility for priority reviews once they become available.

FDA also updated the prioritization MaPP in 2016 to add ANDAs for sole-source drugs, i.e. those with only one manufacturer in the marketplace. It was not expected to have a large impact on generic entry. *(Also see "Drug Pricing Panacea Or Just PR Victory? Expedited ANDAs May Have Limited Impact" - Pink Sheet, 21 Mar, 2016.)*

SHORT-TERM VERSUS LONG-TERM BENEFITS

Kurt Karst, director at Hyman Phelps and McNamara, said in an interview that the new policy "is another piece of the puzzle" and certainly will not address the entire drug pricing problem.

He also said the agency is starting from

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Year's Delay Possible For Europe's Unified Patent Court As German Ratification Is Put On Hold

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Plans to bring Europe's new Unified Patent Court system into operation could be delayed for more than a year following a legal challenge to Germany's ratification of the UPC Agreement that could have knock-on effects in the UK.

BeNeLuxA Medicine Access Collaboration Plans Joint Horizon Scanning

https://pink.pharmamedtechbi.com/PS120985

Belgium, the Netherlands, Luxemburg and Austria are continuing their collaboration on improving access to medicines and are finalizing a proposal on a joint horizon scanning initiative.

EMA Seeks Clarity On Generics Of Drugs Approved Under Exceptional Circumstances

https://pink.pharmamedtechbi.com/PS120994

The European Medicines Agency has asked the European Commission to clarify whether generics of drugs authorized under exceptional circumstances should be subject to the same obligations as the reference product.

When Will Real World Evidence Be Persuasive? FDA's Temple Offers Perspective

https://pink.pharmamedtechbi.com/PS121006

Postmarketing studies randomized to look at real world data sets could provide the key, Temple suggests; Amgen rep describes use of real world data to support approval of leukemia drug Blincyto.

Drug Pricing Hearing In Senate Postponed, Handing Innovators Another Victory

https://pink.pharmamedtechbi.com/PS121002

First hearing in Sen. Alexander's committee was dominated by Democrat complaints about Obamacare repeal; now that there's an actual bill to criticize, the next one might have been even worse, but regardless of the reason, the postponement means innovator prices get to stay out of the spotlight once again.

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scratch with the expanded prioritization policy and expected that it will "take some time before we see the fruits of this."

Karst argued sponsors and FDA must boost the first cycle approval rate to make a priority review a substantial advantage. At first, an eight-month review simply may mean receiving a complete response letter sooner, but eventually, it could mean an earlier launch date.

"Down the road, the expectation is you will have a massive change and will have a lot of ANDAs approved on the first cycle," Karst said.

Flanagan said that there can be a short-term impact because several pending ANDAs have been through a few review cycles already and are close to approval. Upon resubmission, those could be eligible for priority review, he said. Deficiencies also will arrive quicker for priority applications, allowing for faster corrections.

Ultimately, as with most drug pricing-policy moves FDA has made, success likely will depend on industry.

Sponsors still must submit quality applications in order to gain quick approvals. Recent evidence suggests that first-cycle approvals remain a small percentage of OGD's review output. *(Also see "ANDA Approval Times Get Optimistic Estimate In Budget Request" - Pink Sheet, 26 May, 2017.)* FDA would prefer that most ANDAs require two review cycles to gain approval, rather than three or more. *(Also see "ANDA Reviews: First-Cycle Desired, But Two-Cycles OK?" - Pink Sheet, 27 Jul, 2015.)*

With generics becoming a prominent part of the administration's approach to drug pricing, the agency's handling of ANDAs may come under further scrutiny. A just-issued report by the Government Accountability Office summarizes a core dilemma for the program in its title: "Generic Drug User Fees: Application Review Times Declined, but FDA Should Develop a Plan for Administering Its Unobligated User Fees."

TRADE GROUP 'ENTHUSIASTICALLY' EMBRACES NEW POLICY

For ANDA sponsors, FDA's change in ANDA prioritization is significant, because it expands the potential pool of applications that could qualify for priority review.

> "Down the road, the expectation is you will have a massive change and will have a lot of ANDAs approved on the first cycle."
> – attorney Kurt Karst

The Association for Accessible Medicines, which represents the generic drug industry, said in a tweet that it "enthusiastically applauds" the policy change.

AAM President and CEO Chip Davis said in a written statement that Gottlieb's "swift and decisive action" will provide a "tremendous benefit" for patients.

"Today's announcement signals that any serious effort by the Trump Administration or the United States Congress to bring down drug costs for patients must include more affordable generics and biosimilars," he said.

Data suggests that there is a meaningful impact on a drug's price once three generics are approved. By acting quickly on more than just the first filer, prices could drop faster.

The potential advantage is one that some in Congress have already recognized. Sens. Susan Collins, R-Maine, and Al Franken, D-Minn., co-sponsored legislation that would require a priority review for generic applications for products with three or fewer approved applications or listed on the drug shortage list. It was included in the Senate version of the user fee reauthorization legislation. *(Also see "Generic Priority Review Expanded In Senate User Fee Bill" - Pink Sheet, 11 May, 2017.)*

The change also could push OGD's approval volume higher. It has been on the rise in recent months, but stakeholders agree it must go higher for the agency to gain a handle on its generic workload. *(Also see "ANDA Submissions Continue Yo-Yo Pattern, Unlike Approvals" - Pink Sheet, 10 May, 2017.)*

It is unclear whether Congress will make any drug pricing-inspired changes beyond encouraging generic competition. The Senate Health, Education, Labor and Pensions Committee has started a series of hearings on the subject. *(Also see "Drug Pricing 'Deeper Dive' Planned By Senate Cmte. As Industry Avoids First Blood" - Pink Sheet, 14 Jun, 2017.)*

GOTTLIEB RAISES SIMILAR DRUG PRICING THEME IN ANNOUNCEMENT

In addition to the prioritization MaPP change, the agency also published a list of off-patent, off-exclusivity brand products without approved generics in the hopes of attracting more competition.

In a statement announcing both items, Gottlieb used language similar to his first speech before FDA staff after being sworn in, reiterating that "no patient should be priced out of the medicines they need."

Gottlieb also suggested FDA may not be finished working on the issue. "I am committed to continuing to pursue additional policy steps, under the FDA's current authority, to help reduce the burden on patients who have a difficult time paying for the medicines they need," he said.

The agency has shown a willingness to increase its flexibility with complex generic approvals, in part because of the drug pricing issue.

Gottlieb said he may try to adjust regulations on delivery device instructions for use to ease the burden for generic approval. OGD staff also seem open to device variations for generic applicants, but are concerned about patient safety. *(Also see "Generic Combination Products May Be Permitted Delivery Device Variations" - Pink Sheet, 4 Jun, 2017.)*

President Trump also may include generic approval and other policy changes in an executive order on drug pricing that is expected soon. *(Also see "Complex Generics May Be Part Of White House Drug Pricing Response" - Pink Sheet, 22 Jun, 2017.)*

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FDA's Budget Flat In House Bill, But Path For 'Cures' Funding Cleared

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A US House subcommittee adopted a fiscal year 2018 funding measure that would maintain FDA's non-user fee appropriations at the current level while also clearing the way for the agency to receive from the National Institutes of Health funds authorized under the 21st Century Cures Act.

On June 28, the House Appropriations Committee's agriculture subcommittee unanimously voted to send to the full committee a measure that would provide FDA with $2.76bn in discretionary funding for the fiscal year beginning Oct. 1, an amount equal to the FY 2017 level. Total agency funding, including user fee revenue, would be $5.2bn, $490m above the current-year level, the committee said.

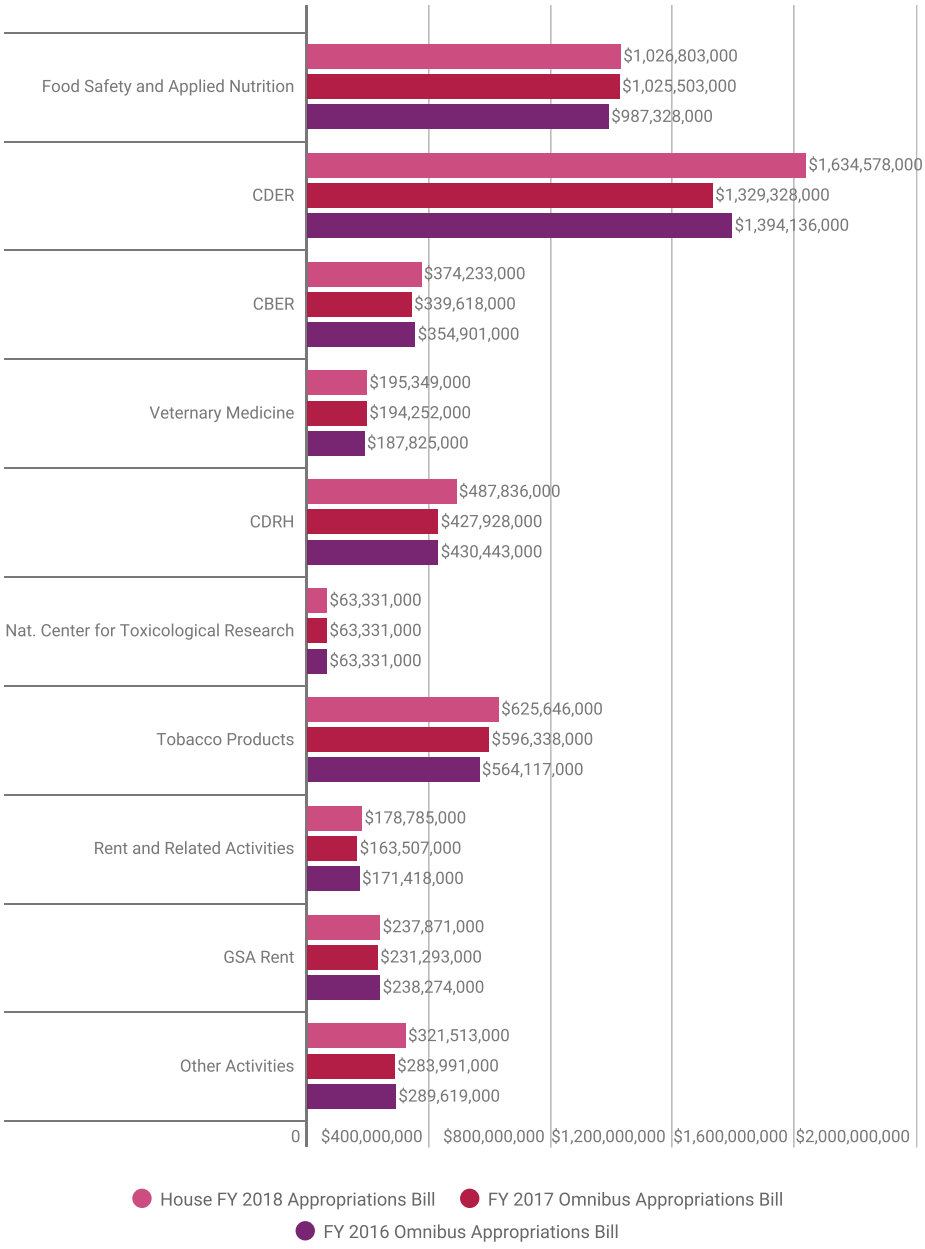
The Center for Drug Evaluation and Research would be allocated $1.63bn, a 23% increase, and the Center for Biologics Evaluation and Research would get $374.2m, a 10% increase. The higher funding levels are due, in part, to expected increases in user fee revenue.

In proposing to maintain FDA's current-year budget authority, House appropriators eschewed President Donald Trump's request to slash the agency's FY 2018 appropriations by 31% while boosting user fee revenue by 68%. *(Also see "FDA Safety Initiatives Could Suffer Under Trump's Budget Proposal" - Pink Sheet, 23 May, 2017.)*

The president's budget request, which would have changed the five-year user fee agreements that are currently awaiting final legislative passage, was widely disparaged by lawmakers at a May 25 hearing. Even FDA Commissioner Scott Gottlieb declined to address the president's proposal, which would have required the reopening of user fee agreements negotiated between FDA and industry. *(Also see "Gottlieb Distances Himself From Trump's User-Fee Heavy Budget" - Pink Sheet, 25 May, 2017.)*

"The bill does not accept the proposed user fee recalibration," Subcommittee

Center Allocations In Recent Appropriations Bills



FDA's non-user fee dollars would not change in FY 2018 under the bill reported by the House Appropriations Committee Agriculture Subcommittee June 28 (top chart). But the centers for drug evaluation and research, biologics evaluation and research, and devices and radiological health would see increases in their overall allocations compared to the FY 2017 omnibus appropriations legislation, in part because user fee dollars are expected to rise.

> The subcommittee's bill would appropriate an additional $60m to FDA as authorized under the 21st Century Cures Act.

Chairman Robert Aderholt, R-AL, said at the markup.

The Alliance for a Stronger FDA said its members were grateful that the House retained FDA's FY 2017 funding base and supported the previously agreed-upon user fee agreements reflected in the FDA Reauthorization Act (FDARA) legislation making its way through the House and Senate.

"While we are grateful to the subcommittee for its support of FDA, we look forward to continued fruitful discussion with the Congress about FDA's increasing responsibilities and the pressures on the agency to build and retain critical medical and scientific personnel," said Cynthia Bens, the Alliance for a Stronger FDA's immediate past president and vice president of public policy at the Alliance for Aging Research. "We are particularly concerned that there be funding to pay for new non-user fee activities contained in the pending FDARA legislation."

CLEARING THE WAY FOR CURES MONEY FROM NIH

The subcommittee's bill would appropriate an additional $60m to FDA as authorized under the 21st Century Cures Act, which was signed into law in December. FDA was appropriated, and has received, $20m in Cures money for FY2017, the agency said.

The House bill includes important language that addresses a limitation in the Cures law by enabling FDA to receive funds transferred from NIH to support the establishment of the Oncology Center of Excellence (OCE).

The Cancer Moonshot section of Cures did not provide direct appropriations for OCE. While funds were authorized to be appropriated to the NIH Innovation Account for the purposes of carrying out activities related to cancer, specific statutory authority is required to transfer resources from one agency to another, and there was no express authority to transfer the funds from NIH to FDA for purposes of supporting the OCE.

The FDA funding bill marked up by the House subcommittee contains that transfer authority, although similar language must also be included in a separate funding measure for NIH, a source said.

FDA has been using existing agency funds to support OCE's establishment and operations. *(Also see "US FDA Still Waiting For Cures Money, Woodcock Says" - Pink Sheet, 25 Apr, 2017.)*

Under Cures, FDA was targeted to receive $15m a year for five years for OCE but has not received the FY2017 installment from NIH because of the transfer issue, according to Ryan Hohman, vice president of public affairs at Friends of Cancer Research.

"Our hope is that [HHS Secretary Tom] Price will allow that to happen so that OCE can get its 2017 funding and support that getting up and running," Hohman said.

RENEWED FOCUS ON OFFICE COMPOUNDING

The subcommittee markup was a brief and largely bipartisan affair. However, some Democratic members' comments suggest the funding measure's consideration by the full Appropriations Committee may be more contentious due to language in a forthcoming committee report.

Rep. Rosa DeLauro, D-CT, said the draft language, which has not been publicly released, would weaken FDA's oversight of pharmacy compounding.

"I'm deeply troubled by the compounding language included in the report that would weaken and undermine the Drug Quality and Security Act (DQSA), an already weak provision made weaker by this report language," DeLauro said. "We cannot afford to lower standards for the compounding industry when the health and the safety of American families is at risk."

Speaking to reporters after the mark up, DeLauro said it appears the draft language would allow for office compounding.

How much authority FDA should exert over compounding of products intended for office stock has been a disputed, gray area since passage of the DQSA. *(Also see "Compounding Oversight May Hinge On How FDA Treats Office Stock" - Pink Sheet, 10 Feb, 2014.)* A provision that attempted to limit the amount of a compounder's total production that could be done for office stock was removed from the final version of the measure. *(Also see "Compounding Deal In Congress Allows Voluntary FDA Oversight Of Large-Scale Facilities" - Pink Sheet, 27 Sep, 2013.)*

A recently introduced House bill, the Preserving Patient Access to Compounded Medications Act (HR 2871), would allow for office-use compounding of medications where authorized by state law, according to the International Academy of Compounding Pharmacists, which supports the measure.

On June 26, FDA's Gottlieb issued a statement emphasizing the importance of the DQSA and highlighting the agency's actions thus far to implement and enforce the law.

"We have taken a risk-based approach to all of these efforts, in order to make sure that we are maximizing the public health purpose of these new provisions relative to the resources we use to achieve them, and any obligations that these new requirements place on market participants," Gottlieb said. "We will continue to actively oversee drug compounders and, when appropriate, initiate regulatory action as it fulfills the FDA public health mission on behalf of patients."

FDA issued the statement the same day the owner and head pharmacist of New England Compounding Center was sentenced to nine years in prison in connection with the 2012 nationwide fungal meningitis outbreak that resulted in 64 deaths.

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ANALYZE

Visit our website at **http://bit.ly/2uovP9m** to access additional data on **FDA's Budget Authority Total Stalls In FY 2018**

ASIA EXECUTIVES TO WATCH: New FDA China Director Named Amid ICH Push

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The US FDA has been quietly stepping up its efforts to work more closely with its Chinese counterpart, the China FDA, the latest move being the appointment of a new director to China, Julio Salazar, who succeeds Leigh Verbois.

Verbois took over the position two years ago, during which the relationship between the two agencies has become closer. *(Also see "FDA Tip-Toes In China To Push Data Integrity, Harmonization" - Pink Sheet, 25 May, 2017.)*

Salazar was formerly the FDA country director for Peru, based in Lima, and before that, he worked at the FDA's Southwest Import District, based in Texas.

With the recent move by China to join the ICH regulatory harmonization initiative, it appears likely that even closer collaboration between the CFDA and its global counterparts will be needed.

Verbois' predecessor Chris Hickey now works for **Pfizer Inc.** as the senior director of Public Affairs, Asia Pacific, but it is not known whether Verbois will also join the private sector or take another position somewhere at the FDA.

CFDA

Meanwhile, the CFDA has a new director of its Center for Medical Device Evaluation (CMDE), Sun Lei. In a series of other new appointments at the center, other new CMDE officials have been named. *(See chart.)*

COMPANIES

Biopharma incubator and investment firm ShangPharma Innovation (SPI) has announced the appointment of Peter DiLaura, Ravi Kiron, Krishna Kodukula, and Robert Wild to its founding Executive-In-Residence (EIR) team.

Per the company, the team will provide expert advice on business, scientific, and strategic development of biomedical initiatives, including the identification and assessment of novel opportunities for early-stage equity investments, and new venture incubator tenants at SPI's South San Francisco facility. They will also participate in the negotiation and management of collaborations, licenses, and partnerships.

David Harrison has started a new position as Business Development Lead at **C4X Discovery Holdings PLC**. He was previously the Senior Business Development Consultant at **Mundipharma International Corp. Ltd.**

INVESTMENT

Lijun Peng has become the Managing Director, Healthcare at China eCapital Corporation. Peng was formerly Director of business development at **Luye Pharma Group Ltd.**, and later became the deputy general manager in the international department at Zhongfa, a domestic conglomerate.

From the editors of PharmAsia News. Published online June 26, 2017

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NAME	NEW POSITION	BUREAU
Wu Kun	Deputy office administrator	
Wu Jianxiong	Deputy Director	General Business
Liu Zhitao	Deputy Director	General Business
Yang Pengfei	Deputy Director	Review Div. 1
Peng Liang	Deputy Director	Review Div. 1
Guo Zhaojun	Deputy Director	Review Div. 2
Zhao Peng	Deputy Director	Review Div. 3
Chen Maobo	Deputy Director	Review Div. 3
Liu Yinghui	Deputy Director	Review Div. 4
Guo Yajun	Deputy Director	Review Div. 4
Yang Xiaodong	Deputy Director	Review Div. 5
Dong Jingcun	Deputy Director	Review Div. 6
Lv Yunfeng	Deputy Director	Review Div. 6

Source: CFDA

EU To Defer US GMP Inspections Ahead Of Mutual Recognition Agreement Becoming Operational In November

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The European Medicines Agency says it will make efforts to defer any good manufacturing practice inspections in the US in anticipation of the EU-US mutual recognition agreement coming into operation from Nov. 1 onwards. The agreement, when operational, will allow drug regulators in the two regions to rely on each other's GMP inspections conducted within their respective territories.

The EMA told the *Pink Sheet* that the "EU inspectorates will be making maximum use of existing EU procedures to defer inspections, where possible, in anticipation of the operational phase of the MRA that starts in November 2017". *(Also see "US Reliance On EU Drug Facility Inspections Begins In November" - Pink Sheet, 5 May, 2017.)(Also see "EU, US Finally Agree On Mutual Recognition Of GMP Inspections" - Pink Sheet, 2 Mar, 2017.)*

Before the MRA can become operational, the EU must have completed its assessment of the US Food and Drug Administration's inspection capabilities by July 1, 2017 (under Article 6 of the agreement). The EMA explained that the European Commission will send a formal notification to the FDA that this obligation has been met.

The FDA, on the other hand, also needs to assess the inspection capabilities of at least eight EU member states by Nov. 1 and formally notify the EU about this. It has until July 15, 2019 to complete its assessment of all the EU member states.

If the FDA is unable to complete the capability assessments of the eight member states by November, then the formal recognition of inspection reports would be delayed until this obligation is met, the EMA explained.

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While 11 member states have submitted complete assessment packages, 17 have yet to do so.

The EMA said that the FDA had not formally notified the EU of the completion of any capability assessments so far, whether positive or negative, as there is no obligation for the US to do so before the November deadline. However, the EMA says it is aware that capability assessments are ongoing and, to date, the EU has complied with the deadlines for submission of assessment packages to help the FDA with its assessment process.

While 11 member states have submitted complete assessment packages, 17 have yet to do so: Belgium, Bulgaria, Cyprus, Germany, Denmark, Estonia, Finland, Ireland, Lithuania, Luxembourg, Latvia, Poland, Portugal, Slovakia, Netherlands, Romania and Slovenia.

The EU-US MRA on GMP inspections will allow both EU inspectors and the FDA to make better use of their inspection resources and focus their limited inspection resources on other parts of the world.

In 2016, EU inspectors undertook 129 GMP inspections in the US. The EMA clarified that the MRA does not cover all product types and makes a number of provisions that uphold the right of either party to conduct its own inspections "but the intention is that EU GMP inspections in the US will be limited."

The EMA could not provide data on how many US GMP inspections, if any, have been undertaken by EU inspectorates since the mutual recognition agreement was signed in March. Since it takes around up to 90 days between an on-site inspection and its conclusion (i.e., the issuing of a GMP certificate or non-compliance statement) being uploaded on the EU GMP database (EudraGMDP), the EMA said it could not provide any hard data on this topic.

From the editors of Scrip Regulatory Affairs.
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Biosimilars In EU: From 'New Mess' To Beacon For Safety

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When the biosimilar regulatory framework was first introduced in the European Union (EU) in 2004, the whole thing was a "new mess," says Finnish Medicines Agency senior researcher Niklas Ekman.

"Industry didn't know how to do things," Ekman said June 26 at the 2017 Parental Drug Association/US FDA Biosimilars Conference. "We as regulators did not know how to regulate them."

Since then, however, the EU has approved more biosimilars than anywhere else in the world, 28 to be exact, with the first coming in 2006. With those approvals, there have been no relevant differences observed in adverse events between the biosimilars and their reference products," according to Ekman.

Despite the initial difficulties, "we succeeded," Ekman says. "Nothing really has happened in the 10 years. So we have done a good job, both industry and regulators."

There are also several more biosimimlars in the EU's pipeline. The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) just recommend approval of another biosimilar version of **AbbVie Inc.**'s TNF-alpha inhibitor, *Humira* (adalimumab), this one from **Samsung Bioepis Co. Ltd.***(Also see "EU CHMP OKs Imraldi, Samsung Bioepis' Biosimilar Of AbbVie's Humira" - Pink Sheet, 26 Jun, 2017.)*

Boehringer Ingelheim GMBH also has filed its Humira biosimilar BI 695501 for approval in the EU, as well as the US. The company recently presented pivotal Phase III results for the biosimilar at the Annual European Congress of Rheumatology (EULAR).

ROOM FOR IMPROVEMENT

Ekman says one area where European regulators have been criticized a lack of a regulatory process to provide data-driven advice to sponsors.

In response, EMA launched a tailored scientific advice pilot project to support the development of new biosimilars in February 2017. The pilot specifically deals with scientific advice relating to quality aspects, and companies can get extended advice about their data that will help them plan future product development and prepare better for a marketing authorization submission. *(Also see "Biosimilars Get Bespoke Service: EMA To Pilot Tailored Scientific Advice" - Pink Sheet, 28 Dec, 2016.)*

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> EMA launched a tailored scientific advice pilot project to support the development of new biosimilars in February 2017.

Ekman, however, says there have been "surprisingly few" companies who have participated in the pilot so far. "I would have expected much more companies," he said. "I think this is a really important thing."

CONNECTING WITH PRESCRIBERS ALSO DIFFICULT

Another area Ekman says needs work is making prescribers comfortable with biosimilars. Prescribers are "extremely concerned," about biosimilars, and industry and regulators need to work in conjunction to ease their fears.

Steven Kozlowski, a supervisory medical officer in FDA's Center for Drug Evaluation and Research (CDER), agreed that the same problems with consumers and prescribers also exist in the US, in that "there is not necessarily a full understanding of these products."

"I think the focus that they are still seeing this as safety and efficacy for the biosimilar on an independent evidence screen as opposed to biosimilarity of the evidence that needs to be generated," Kozlowski said. "And that leads to safety and efficacy of that product."

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EFPIA Calls For Interim Accords To Ease Brexit Impact

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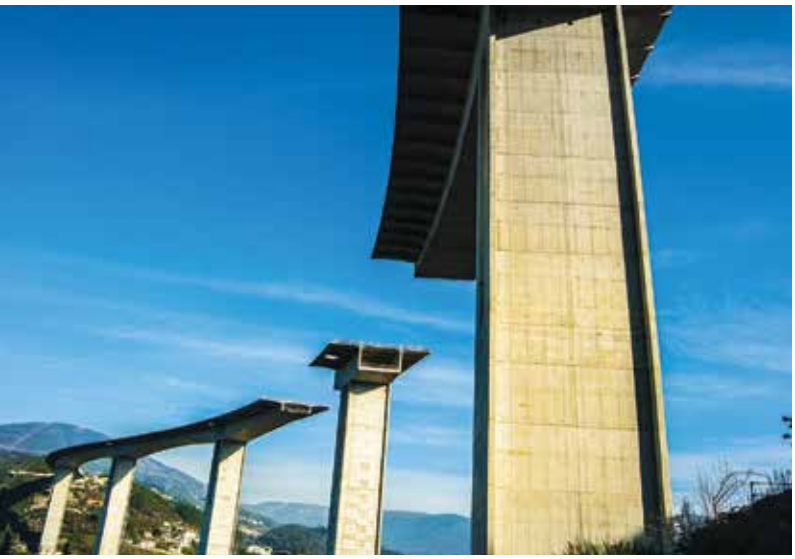

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While the initial talks about Brexit will focus on its political implications, and establishing frameworks for the negotiations, the uncertainty for the pharmaceutical sector caused by the UK's decision to leave the EU has to be addressed without any more delays "and the first phase, the divorce phase, needs to be as quick as possible," says Elizabeth Kuiper, director of European affairs at the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Speaking to *Scrip* at EFPIA's annual conference in Brussels last week, Kuiper said that now Article 50 has been triggered, "the clock is ticking" as the withdrawal of the UK from the EU begins.

TRANSITIONAL AGREEMENTS

EFPIA understands the talks will be long, but the industry body is pushing for "transitional agreements" that will limit disruption, Kuiper said. "Our sector is not like any other; we are about patient safety and we need continuity from day one, when the UK leaves," she argued.

Kuiper went on to note that there are a host of issues still up in the air, concerning regulation, the pharmaceutical supply chain, intellectual property, pharmacovigilance, falsified medicines and disease control, to highlight just a few. To deal with these, the EU has benefited from strong and very successful frameworks for decades "and we need to keep the quality of those frameworks."

EFPIA is particularly concerned about what effect the UK departure will have on research, notably through the federation's €3.3bn public-private partnership with the European Commission, the Innovative Medicines Initiative 2. Half of that budget comes from the EU's vast Horizon 2020 research fund, "in which the UK plays a big part," Kuiper stated, "and we will lose a lot of input if the UK's scientific community can't participate."

CONCERN OVER FUTURE MHRA INPUT

On the regulatory front, she said clarification was needed regarding the European Medicines Agency's relationship with the UK's Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA's input to the centralized approvals procedure accounts for 25-30% of evaluations and 40% in the decentralized procedure – and EFPIA is keen to see what the MHRA's future contribution to regulatory reviews is going to be.

As for the best place to relocate the headquarters of the EMA, Kuiper would not be drawn on expressing a preference (although a *Scrip* straw poll at the EFPIA conference put Copenhagen in pole position, followed by Dublin).

She reiterated the association's desire for a quick decision so as not to disrupt the EMA's work too much. "We need to end the uncertainty," she concluded. Member states need to submit their bids by July 31 at the latest, and the winner is due to be unveiled in November. *(Also see "EU Postpones Decision On EMA's New Home To November" - Pink Sheet, 23 Jun, 2017.)*

From the editors of Scrip Regulatory Affairs. Published online June 23, 2017

FDA's Definition of Statistical Significance: P=.05 – ish

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When **Portola Pharmaceuticals Inc.** announced the results of a Phase III trial of its proposed anticoagulant betrixiban last March, the headlines were brutal.

"Portola's long-acting blood thinner misses main goal in study," Reuters headlined its March 24 story. "Portola stock bleeds with latest drug study results," Forbes chimed in the same day.

That's what happens when large randomized trials fail to demonstrate a statistically significant treatment effect. And, as the stories duly reported, Portola's APEX trial in 7,500 patients came agonizingly close to the conventional p=.05 threshold for statistical significant, with a reported p-value of .054.

If you haven't paid attention since, you would be quite surprised to learn that betrixiban received FDA approval (under the brand name *Bevyxxa*) based on the APEX results just 15 months later, on June 23. That would count as a rapid turnaround from trial completion to FDA approval for any drug – much less for one that "failed" in Phase III *(Also see "Keeping Track: Cardio, Antibiotic Approvals Put FDA Over Last Year's Novel Drug Count" - Pink Sheet, 26 Jun, 2017.)*.

Of course, as FDA's approval makes clear, it turns out that *Bevyxxa* did not "fail" in its Phase III trial, despite the p-value. And that is a timely reminder that treating statistical significance tests as a "pass/fail" question isn't exactly right.

By coincidence, FDA Center for Drug Evaluation & Research Director Janet Woodcock appeared at a New York Academy of Sciences meeting on June 22 to discuss modern trends in clinical development, and spoke directly to the misunderstanding of the p-value as it relates to regulatory decision-making.

She started by describing randomization in clinical trials as a "useful tool," but emphasized that it is "not mandatory" and indeed "not always possible." Thus, FDA has and will approve drugs based on single-arm and/or open-label trials.

Broadly speaking, FDA welcomes "a multitude of trial designs," FDA's Woodcock says, and highlights a number of strategies that have emerged from oncology trials as potential models.

"Similarly, the p-value .05 is an arbitrary threshold," Woodcock said. "I think we've passed into not thinking about this correctly, and I think most statisticians think this too. It is not a pass/fail boundary, except in a regulatory sense, an arbitrary sense. It doesn't mean what most people believe it means."

Rather than look solely at the p-value, the question is "what is the robustness of an evidence of an effect?" That can include things like the "mechanistic evidence" if there is any, she noted. And, stressing a point she made most clearly in the context of the contentious review of Sarepta's DMD therapy *Exondys 51* (eteplirsen), Woodcock added the importance of asking: "If this effect is one that matters, what would be the impact of failing to provide this benefit if the benefit really exists?"

That point "is highly neglected in the conversations," Woodcock said, which (in her view) usually stress the harm from approving a dangerous or ineffective drug, not the harm from withholding an effective one.

Broadly speaking, Woodcock added, FDA welcomes "a multitude of trial designs," and – not surprisingly –highlights a number of strategies that have emerged from oncology trials as potential models (like master protocols and basket trials).

Woodcock's general observations help explain the approval of betrixiban.

First, on the robustness of the evidence: the primary analysis did fail on the conventional test of statistical significance but it was right on the line. In addition, two "secondary" analyses showed effects that did beat the p=.05 population – and, unlike most study designs, the secondary analyses actually included more patients than the primary analysis. (The "primary" analysis was in a subgroup of the total patient population where Portola incorrectly expected benefit to be most clear.)

Moreover, this was not a placebo-controlled study: Portola compared "extended duration" use of betrixiban (35-42 days) versus standard, short-term use of enoxaparin (6-14 days). So, while there may be room to debate whether the drug is statistically "better" than enoxaparin, it is harder to argue that it is ineffective given enoxaparin's known benefit.

In addition, there is mechanistic data to support the drug: it is a Factor Xa inhibitor, a class with multiple entrants (including *Xarelto* and *Eliquis*).

And then there is the perceived medical need. FDA granted Portola priority review for the proposed indication in patients hospitalized long term with limited mobility or other high risk factors for a thrombotic event. At a minimum, FDA agreed that there are consequences to denying an effective therapy to those patients.

Last but not least, there is the connection to the oncology review group. Like all anticoagulants for DVT, it was reviewed and approved by the Office of Hematology and Oncology Products at FDA – and the approval letter was signed by OHOP Director Richard Pazdur.

From the editors of the RPM Report.
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Big REVEAL: Merck's Anacetrapib Surprises With Success, But What Next?

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Merck & Co. Inc. may have beat the odds and breathed new life into the CETP inhibitor class with the demonstration of a cardiovascular outcomes advantage for its anacetrapib in the 30,000-patient REVEAL trial, but the company seems uncertain of its next steps.

Merck has said merely that it planned to review the REVEAL results of the trial with external experts, and would "consider whether to file new drug applications" with the FDA and other regulatory agencies.

The company announced June 27 that the CVOT study had met its primary endpoint, significantly reducing major coronary events (a composite of coronary death, myocardial infarction, and coronary revascularization) compared with placebo in patients at high risk for cardiac events who are already receiving atorvastatin.

No further details were released except that to say that so far, the drug's safety profile was generally consistent with that seen in its previous studies, including an accumulation of anacetrapib in adipose tissue. The full results of the four-year study will be presented at the European Society of Cardiology meeting on Aug. 29.

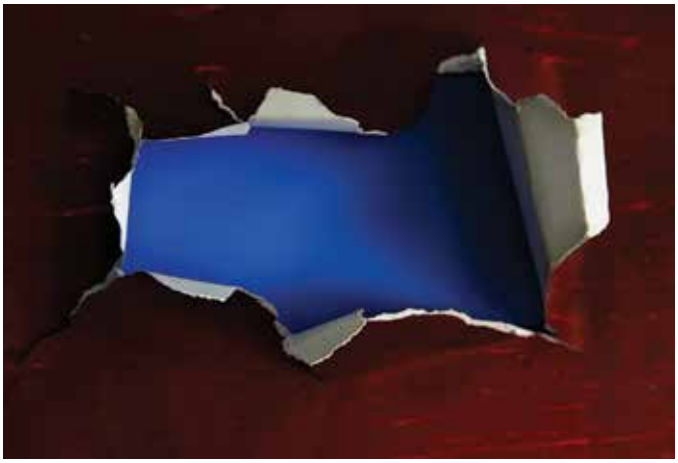
Merck's reticence to confirm regulatory plans was pounced upon by analysts. "The cryptic language in the press release suggests a less than definitive risk/reward profile of the drug," Leerink Swann's Seamus Fernandez said in a June 27 note.

Tim Anderson at Bernstein said that their best guess as to potential issues related to two things: anacetrapib's very long half-life, which means it accumulates in tissues, such as adipose tissue; and the size of its effect on heart attack rates, which they suggest may not be clinically meaningful.

"If anacetrapib ends only up looking like a weak LDL-lowerer (without any clear clinical benefit coming from the HDL raising it also causes), because of the tissue accumulation issue and the presence of generic cholesterol drugs (statins, and even Merck's own *Zetia*), then the company might reason that the commercial case to file for approval is a weak one," Anderson said.

Fernandez was also worried at the mention of accumulation in adipose tissue. "We believe the mention of this highlights a potential long-term regulatory concern – one that we believe would require a very robust impact on key CV events – like death – for [Merck] to file anacetrapib," he commented.

The size of the trial means both that it's enough to provide a definitive answer on anacetrapib, but also that even a small effect could be statistically significant, Fernandez pointed out. "We estimate this could be a relative risk reduction well below 10%, which we would argue is not clinically significant unless the benefit was driven almost entirely by CV death," he said. "We remain skeptical of the opportunity for anacetrapib and believe the risk of launching this drug given potential safety uncertainty around accumulation in adipose tissue may substantially outweigh the product's value."



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> "Overall, we get a sense that the magnitude of benefit is likely modest," Evercore ISI's Raffat said.

But Umer Raffat from Evercore ISI believes Merck should take a punt anyway. "In fact, I would argue: why not? (especially after spending hundreds of millions on this trial and meeting primary endpoint). Ultimately, there is a need for added control beyond statins … if you need modestly more benefit, you could consider *Vytorin* and now anacetrapib … if you need MUCH more LDL benefit, you could consider PCSK9s," he said.

DIFFERENCES IN THE MOLECULES

Merck may wind up proving that slow and steady wins the race. The cholesteryl ester transfer protein class was once hailed as the natural successor to the statins, but **Pfizer Inc.**'s dramatic discontinuation of the first CETP inhibitor torcetrapib – and the subsequent failure of other candidates – raised huge doubts about the mechanism.

Pfizer's pioneering product torcetrapib was dropped back in 2006 after an increase in CV death despite an increase in the "protective" HDL-cholesterol with the product, but it was hoped that the problem lay with the drug molecule itself rather than with the mechanism more broadly. Other later trials also raised questions about the benefit of raising HDL, but anacetrapib – the first CETP inhibitor to show an effect on CV outcomes – also has LDL lowering effects.

Development of other CETP inhibitor candidates continued after Pfizer's failure, only for them to fall along the way – **Eli Lilly & Co.** ended the Phase III program for its evacetrapib in late 2015 after the 13,000-patient ACCELERATE CVOT study was stopped

for futility. *(Also see "Who Suffers From Lilly's Evacetrapib Failure?" - Pink Sheet, 12 Oct, 2015.)* And **Roche**'s dalcetrapib failed in the dal-OUTCOMES trial in 2012 although this product has since been acquired by **DalCor Pharmaceuticals**, which is hoping to find a genetic marker to keep it alive. *(Also see "Out Of The Ashes: Roche's Dalcetrapib Data Suggest Still Hope For CETP Inhibitor Class" - Pink Sheet, 12 Nov, 2012.)* Also still in development is **Amgen Inc.**'s AMG-899 at the Phase II stage.

Many believed that Merck's continued development of anacetrapib would prove a costly distraction, but others were less pessimistic. "We have long maintained that the market was overly negative on the odds of anacetrapib working," Anderson declared in a June 27 note. "This is because the first two failed CETP inhibitors had no LDL effect (they only raised HDL) – by contrast, Lilly and Merck's drugs both raised HDL and lowered LDL. And Lilly's drug was studied in a much smaller, shorter trial than Merck's, and also in a slightly different patient population – this was Lilly's attempt to yield results more quickly than Merck, but the strategy backfired."

MUCH REMAINS TO BE SEEN

A lot will rest on the size of the benefit seen when the full data are released, and by extension the commercial upside for Merck, given that most observers had expected the trial to fail.

In this, its comparison with Vytorin's effect in IMPROVE-IT will be illustrative. While the CETP inhibitors were moving through the clinic (mostly to oblivion), Merck had success with the major CVOT trial for its older combination dyslipidemia product Vytorin (ezetimibe/simvastatin) – showing a more than 6% benefit and hitting statistical significance in the 18,000-patient study. However, the data did not convince the FDA to add the CV risk reduction claim to its label. *(Also see "FDA's Zetia/Vytorin Rejection Leaves Cholesterol Drug Sponsors In Limbo" - Pink Sheet, 16 Feb, 2016.)* Although sales for the Zetia/Vytorin franchise have slackened recently, revenues for 2016 still hit $3.7bn.

> Merck may wind up proving that slow and steady wins the race. The CTEP class was once hailed as the natural successor to the statins, but Pfizer's dramatic discontinuation of the first CETP inhibitor torcetrapib and the failure of other candidates raised huge doubts about the mechanism.

Raffat points out that while REVEAL was powered to show a 15% relative risk reduction, the fact that it has met its primary endpoint does not mean that it was as effective as this. "REVEAL is an even bigger trial [than IMPROVE-IT] … so perhaps it could have hit [statistical significance] at as low as about 5% potentially," Raffat said. "Overall, we get a sense that the magnitude of benefit is likely modest … perhaps in single digits."

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NEW PRODUCTS

FDA's NDA And BLA Approvals: Bevyxxa

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				
Portala	*Bevyxxa* (betrixaban)	Prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE. *Also see "FDA's Definition of Statistical Significance: P=.05 – ish" - Pink Sheet, 26 Jun, 2017.)*	P, 1	6/23/2017

KEY TO ABBREVIATIONS

Review Classifications	NDA Chemical Types
P: Priority review **S:** Standard review **O:** Orphan Drug	**1:** New molecular entity (NME); **2:** New active ingredient; **3:** New dosage form; **4:** New Combination; **5:** New formulation or new manufacturer; **6:** New indication; **7:** Drug already marketed without an approved NDA; **8:** OTC (over-the-counter) switch; **9:** New indication submitted as distinct NDA – consolidated with original NDA; **10:** New indication submitted as distinct NDA – not consolidated with original NDA

Gene Therapy Reimbursement: Is Blindness A Bad First Test?

LAURA HELBLING pinkeditor@informa.com

Spark Therapeutics Inc.'s voretigene neparvovec is pending at FDA for treatment of a rare form of hereditary blindness and seems likely to become the first-ever gene therapy approval in the US. By default, it will then become the test case for how reimbursement and coverage policy works in the context of gene therapy.

However, **Express Scripts Holding Co.** Chief Medical Officer Steve Miller told the Biotechnology Industry Organization during its annual meeting in San Diego June 20, one of the features that should help secure FDA approval for the therapy is actually a drawback for payors: the complete lack of alternative therapies.

In the regulatory context, the lack of alternatives makes the efficacy of Spark's product stand out and simplifies the risk/benefit discussion. For payors, however, that means there is no medical cost to offset by paying for a new therapy, leading Miller to suggest that it might be easier if the first gene therapy treats a condition where there already is medical spend, like hemophilia.

In response to a question about the possibility of reimbursing for high-cost gene therapies, Miller noted the lack of medical offset when new therapies treat conditions where there's currently no existing treatment to offset.

Miller threw out an estimate of $ 1 million an eye, or $2 million in new spend per patient for Spark's product. "The question is: are plan sponsors going to be willing to pay $2 million?" Miller said.

"Do not fixate on the idea that all of them [gene therapies] are going to be curative," Miller added. "Some of these are just going to be palliative." In the case of the Spark gene therapy, "these kids can see better, but they still can't see newsprint," he said.

Miller acknowledged that the efficacy benefits are nevertheless dramatic. For example, the vision improvement allows children to walk around a room without an aide or a parent to help. "We're supposed to be in the business of providing better health to people," he said. "So we're going to have to figure out how to pay for that, which means that we've got to cut out every ounce of waste in the system to make sure we have the dollars that are available to pay for it."

"For the other gene therapies, like hemophilia, where we're paying on the average $150,000-$200,000 a person" per year, "even at $2 million, there is going to be an RoI on that," Miller said. "If that was the first one that came to the marketplace it'd be a much easier argument. But the eye one is probably going to be the first gene therapy, it's probably going to happen this year, and we don't have a system that's actually designed to pay for it."

Because the condition is so rare, Miller said, the challenge will not be felt equally by all payors. "I think we will figure out – especially big payers – the Optums, Express Scripts, we will be able to handle this," he said. "For small regional health plans, that's a different issue. If you have a family with multiple kids – that could be a real challenge."

The issues for gene therapy bring to the fore the broader challenges in biopharma reimbursement when companies focus increasingly on smaller populations with significant unmet medical need, rather than on incremental improvements in treatments for more common diseases. The potential price tag (and potential efficacy outcome) may be higher for gene therapies, but the lessons learned will likely be applied to other breakthrough products across the biopharma sector. *(Also see "BIO Notebook, Day 2: Deal Insights, A Payer Perspective And EMA Rumors" - Scrip, 21 Jun, 2017.)*

Amgen Inc. Senior VP Global Value, Access and Policy Joshua Ofman highlighted that broader point during a separate presentation June 21. Biopharma has been innovating – but the payment system has not, Ofman said. Without changes, the concerns won't solely affect gene therapies, but also "any of our genomic or personalized medicine at all."

"Not all medicines ... are going to reduce healthcare costs. They could be prolonging life or improving quality of life or productivity." – Amgen Senior VP Joshua Ofman

The focus on the short term is "tilting and shading the way we think about the potential for innovation," Ofman said. "We should be demanding innovation and applauding it when we get it." Instead "everybody is fearing it, because we just focus on short-term budgets."

Ofman noted that "not all medicines, and not all treatments, are going to reduce healthcare costs. They could be prolonging life or improving quality of life or productivity to massive extents, which have huge social benefits, but not all of our value assessments consider those type of things."

"We assume we know how much we should be spending on medicine," Ofman said. In fact, "we have no idea what the right number is. Maybe we should be spending more. Medicines are the things that are driving the greatest improvements in health right now."

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ICER And The VA: Match Made in Heaven?

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The Institute for Clinical and Economic Review has announced a collaboration with the US Department of Veterans Affairs aimed at supporting the agency's use of ICER prescription drug assessment reports in coverage and price negotiations with biopharma manufacturers.

ICER will help the VA Pharmacy Benefits Management Services office to develop options for using its recommended "value-based price benchmarks" in the contracting process. The VA is already using ICER reports in its coverage policy but will now work with ICER on ways to adapt the findings for the patients it serves and potentially develop new approaches for the future.

"We will work closely with the VA to support its efforts to consider the findings of our reports in the context of its own population," ICER said in a June 27 release.

"We will also assist the VA in exploring new ways it can use the reports to continue to provide a safe, effective and sustainable prescription benefit while more closely aligning a drug's price with the value it provides to veterans and the US taxpayer."

The collaboration is envisioned as a "two-way street" that will allow ICER to "learn from [the VA] how we can provide the information to compare clinical effectiveness and well as comparative cost effectiveness that can inform their decision-making," ICER President Steve Pearson said in an interview. For example, "we heard feedback from them on the need for how the populations studied [in pivotal clinical trials] had relevance to the VA population."

The VA is well known for extracting significant discounts on the drugs it purchases, so the idea that the agency is potentially looking to do more through a collaboration with ICER may be worrisome to manufacturers. ICER's reports frequently recommend substantial list price discounts for the drugs they cover.

The VA requires manufacturers to provide 24% off a drug's average price – or the lowest price paid by other non-federal purchasers – and additional discounts if a drug's price outstrips inflation. The agency also directly negotiates with manufacturers using access to the VA formulary as leverage, which deepens price concessions. Because those negotiations are private it is not clear how much of a discount the VA ultimately gets.

The VA accounts for a relatively small share of government spending on prescription drugs; in fiscal 2017, the total is expected to be approximately $5.2bn. Still, the agency has been held up as a potential model for prescription drug purchasing by other government entities. For example, California's failed 2016 ballot initiative, Proposition 61, would have cut the state's payments for certain drugs to VA-level prices. *(Also see "California's Prop 61 Fails, But More Pricing Measures Could Be Ahead" - Pink Sheet, 9 Nov, 2016.)*

VALUE FRAMEWORKS HAVE SHORTCOMINGS, NPC WARNS

The National Pharmaceutical Council expressed concern with the collaboration in a statement released June 29. "Today's frameworks are not without their flaws," the group said. A "one size fits all" approach and the fact that frameworks evaluate evidence at a single point in time were two of the issues raised.

Furthermore, "ICER's framework is heavily focused on a health system perspective, as is the VA. But looking through the health system lens alone minimizes the importance of societal benefits and costs and their impact on patients' lives," NPC warned.

"It's incumbent upon the VA and ICER to ensure that a broad array of evidence is used and regularly updated, a variety of frameworks and stakeholder input is considered, and the factors that are important to veterans and their families are included in decision-making," the group urged.

SEEKING NEW WAYS TO SAVE?

The collaboration with ICER signals that even the VA is being driven to seek new ways to save on prescription drug costs.

The agency "continually looks for opportunities to leverage existing information that can be incorporated into the formulary decision-making process," VA Pharmacy Benefits Management Services Chief Consultant Michael Valentino told the Pink Sheet. "The robust, timely and high-quality nature of ICER's work is a natural fit for the VA."

"They're looking for new opportunities to be smart, to figure out an explicit, transparent approach to get them further down the road," ICER's Pearson pointed out. "Even with all they're doing they still feel pressure, partly because of the innovative drug pipeline, such as the PCSK9 inhibitors, which offer a lot of opportunity for populations like the VA's" but at a high cost.

ICER recently issued an evidence update to its assessment of **Amgen Inc.**'s PCSK9 inhibitor, *Repatha* (evolocumab). *(Also see "Repatha Pricing Pressure Might Actually Increase After Outcomes Trial" - Pink Sheet, 14 Jun, 2017.)* The group also has evaluated abuse-deterrent opioids, a topic of particular interest to the VA. *(Also see "Abuse-Deterrent Opioids: ICER Value Analysis Could Reinforce Coverage Restrictions" - Pink Sheet, 10 May, 2017.)* ICER's report concludes the data are insufficient to conclude abuse-deterrent formulations are cost effective.

The VA appears to share that view. "VA facilities can use abuse-deterrent opioids if they choose," Valentino said. "However, the evidence of benefit is not convincing. We remain skeptical and believe the increased cost of abuse-deterrent opioids might be better spent on [medication-assisted treatment], inpatient treatment, etc.

"Remember when we were told long-acting opioids weren't addictive, also with no evidence?" he added.

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BeNeLuxA Medicine Access Collaboration Plans Joint Horizon Scanning

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The BeNeLuxA initiative, made up of Belgium, the Netherlands, Luxembourg and Austria, is continuing collaboration on improving access to costly, high-impact medicines and is now finalizing a proposal on how the four countries, and potentially others, could work together on horizon scanning.

The so-called BeNeLuxA Collaboration Initiative focuses on drugs with costs that "are expected to be disproportionately high per year or per treatment, in comparison with other drugs, or which are expected to have a significant overall budget impact," according to the Dutch health ministry.

Horizon scanning is just one of four areas of work that the collaboration is focusing on. The other three are health technology assessment (HTA), information sharing and policy exchange and joint price negotiations. Activities and pilots are ongoing for all four areas. *(Also see "First Benelux Joint Pricing and Reimbursement Pilot Fails Over Vertex' Orkambi" - Pink Sheet, 16 Jun, 2017.)*

Austria is the most recent addition to the collaboration, but according to the Dutch health ministry several countries are interested in joining and discussions with other countries are ongoing. The joint horizon scanning initiative could be open to even more countries, however. The collaboration is extending "an open call" for other countries to take part. This is because the outcomes of horizon scanning are "universally relevant to payers", said a spokesperson from the Dutch health ministry.

The joint horizon scanning proposal is based on a report from the Belgian Healthcare Knowledge Centre on horizon scanning. This report proposes that a central horizon scanning unit should be created to conduct joint activities. This could be a newly established unit within an existing agency in one of the participating countries, or it could be a third party that is commissioned and financed by collaborating countries. This unit would be tasked with identifying and filtering new and emerging pharmaceuticals. It would also maintain and update a horizon scanning database, organize pipeline meetings with companies and disseminate output.

According to the report, the scope of a joint horizon scanning system includes "both inpatient and outpatient pharmaceutical products with a potentially high financial, clinical and/or organizational impact on the health system". This includes the first biosimilar version of a biological product, cellular therapies and/or gene therapies licensed by the European Medicines Agency. Prophylactic vaccines, generics and medical devices are excluded from the scope at the moment.

According to the report, a joint horizon scanning system should incorporate a number of objectives, including:

- informing about new and emerging pharmaceuticals for the purpose of reimbursement decisions and policy development;
- informing decision makers about issues relevant to the managed introduction and monitoring of drugs;
- facilitating budget impact estimates and budget planning;
- allowing the selection of pharmaceuticals for international collaboration on price negotiations, HTA and registers and early dialogue with industry
- planning health services.
- The report points out that there is a "a trade-off between early information, with more uncertainty, and late information with less uncertainty." To strike a balance between different objectives and associated time horizons among the different countries, the report suggests that the report produces three lists of products that are compiled according to the stage of development the drug is at and the impact it is expected to have on the health system.

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Year's Delay Possible For Europe's Unified Patent Court As German Ratification Is Put On Hold

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The committee responsible for preparing the implementation of Europe's Unified Patent Court says it does not know when the new system will enter into force, after Germany's ratification procedure was unexpectedly put on hold pending the resolution of a legal challenge in the Constitutional Court.

The new system had been expected to come into force in December this year, but this will not happen, and the future timetable will depend to a large extent on how quickly the German case can be dealt with. Even if the case is fast-tracked, the Constitutional Court could take up to a year to issue its decision, and it could be "towards the end of 2018 or into 2019" before the new patent system finally comes into operation, according to lawyers at Pinsent Masons.

Germany's delay could also put the brakes on the ratification procedure in the UK, which has said it intends to press ahead and ratify the agreement despite the Brexit vote. The UK situation has been further complicated by political uncertainty following the general election on June 8.

Only a month or so ago, it had seemed that preparations for the new system were progressing well, with both Germany and the UK reported to be nearing ratification. 13 countries, including France, Germany and the UK, must pass national legislation to ratify the UPC Agreement (UPCA) before it can come into effect.

France has already ratified the agreement, and Italy did so in February this year, bringing the total number of signatories to 12.

Moreover, the UK government has just laid down the orders implementing the Protocol on Privileges and Immunities, which signals "a firm intent and commitment on the road to ratification," according to the chair of the UPC Preparatory Committee, Alexander Ramsay, who said in a June 27 statement that Estonia has passed the necessary laws and is taking the final steps towards formal ratification.

But things started to go awry at the end of last month when three of the 13 member states missed the May 29 target date to agree on the Provisional Application Phase for the new system. Unless the 13 countries reached an agreement on the PAP by the summer break, it would be "too late to launch the unitary patent this year," the European Commissioner for the Internal Market, Industry, Entrepreneurship and SMEs, Elżbieta Bieńkowska, said at the time. *(Also see "Preparation Plan For Europe's Unified Patent Court Delayed; UK General Election Spells More Uncertainty" - Pink Sheet, 5 Jun, 2017.)*

The Preparatory Committee then confirmed on June 7 that because of "some delays" to the procedures, including participation in the Protocol on Provisional Application, "the previously announced target date for the entry into operation of the UPC, envisaged for December 2017, cannot be maintained."

> "The UK has shown a firm intent and commitment on the road to ratification" – Alexander Ramsay, chair of the UPC Preparatory Committee

GERMAN SPANNER

Now another major spanner has been thrown into the works after an unnamed individual lodged a complaint against the German ratification bill and sought emergency measures ordering suspension of the process until the Constitutional Court has decided on the merits of the case.

The Constitutional Court "seems to have informed the President of the Republic informally and as seems to be the usual practice in Germany, the President has decided not to proceed with the ratification until the Court has decided on the request for preliminary measures," Ramsay commented.

Details of the reasoning behind the legal case are unclear. Ramsay said it was "difficult to get a clear understanding of what is the status of the suit and what it is about, since there is not much information publicly available. The complaint has not been notified to the German Government or the Parliament."

Marc Holthorf, a life sciences and patent law expert at Pinsent Masons, said: "This is the first case I can recall where a member of the judiciary in Germany has called on the president to delay the adoption of new legislation."

Holthorf said that details of the complainant and the precise grounds for the complaint are not yet known, but that the case "is likely to relate to the fact that the legislation provides for transfer of judicial power away from courts in Germany to a supra-national organisation – the UPC."

In Germany, he said, "anyone can file a constitutional complaint. Every year there are thousands of these complaints that the courts have to deal with, but the vast majority – probably more than 90% - are dismissed at the first stage of proceedings. The fact that this case has been deemed worthy of further consideration is therefore noteworthy."

Given the current situation, Ramsay said it was difficult to give a definitive starting date for the period of provisional application. "However, I am hopeful the situation regarding the constitutional complaint in Germany will be resolved rather quickly and therefore I am hopeful that the period of provisional application can start during the autumn 2017 which would mean that the sunrise period for

the opt out procedure would start early 2018 followed by the entry into force of the UPCA and the UPC becoming operational."

THE INEVITABLE BREXIT FACTOR

However, even this timetable could be on the optimistic side. The UK ratification procedure has already been delayed by the June 8 general election called by prime minister Theresa May. German ratification would have increased the pressure on the UK government to do the same, says Michael Schneider, a patent litigation expert at Pinsent Masons.

Now the uncertainty over Germany's position "may result in the UK further postponing its ratification," Schneider said. "The recent result from the UK general election has created political uncertainty which is unlikely to speed up ratification in the UK, and makes it more likely that its ratification becomes part of broader negotiations with the EU over the terms of Brexit," Schneider declared.

"It now looks increasingly likely that the earliest that the unitary patent and UPC framework could become operational will be towards the end of 2018 or into 2019," he suggested.

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EMA Seeks Clarity On Generics Of Drugs Approved Under Exceptional Circumstances

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The European Medicines Agency has asked the European Commission to clarify how it should handle marketing applications for generic medicines where the reference medicinal product is authorized under exceptional circumstances.

The EMA wants the clarification because certain marketing authorization applications for generics that have been submitted via the EU's centralized procedure and decentralized procedure and are currently under review have used a reference drug that had been authorized under the agency's exceptional circumstances provisions, an EMA spokesperson told the *Pink Sheet*.

Drugs authorized under exceptional circumstances are approved on the basis of less comprehensive data than usand are, as such, subjected to a number of specific obligations that are reviewed annually by the agency's human medicines evaluation committee, the CHMP. These measures are primarily aimed at maximizing as far as reasonably possible the knowledge about the product.

The EMA wants to know "whether specific obligation(s) imposed on the reference medicinal product" should also be required for the generic version of the drug, the spokesperson explained.

It is important to agree "on a common position for such generic products, both at national and centralised level," the EMA said of its consultation on the matter with the commission. The agency noted that it "routinely" discusses matters related to the interpretation of legislation with the commission. The EU Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) is also involved in these latest discussions, and raised the issue at its March meeting.

As for the generic drugs under review that use a reference product authorized under exceptional circumstances, the agency said that the outcome of the review would be communicated once the procedures were complete.

The exceptional circumstances pathway is reserved for medicines for which comprehensive data cannot be obtained even after market authorization. To qualify for this route, the sponsor has to demonstrate that comprehensive data on the efficacy and safety of the drug cannot be provided under normal conditions.

This can happen because: the indications for which the product is intended are encountered so rarely that one cannot be reasonably expected to provide comprehensive evidence; or in the present state of scientific knowledge, comprehensive information cannot be provided; or it would be contrary to generally accepted principles of medical ethics to collect such information. *(Also see "New Standard Of Care Secures EU OK For Neuroblastoma Drug" - Pink Sheet, 24 May, 2017.)*

At the CMDh's March meeting, it was noted that drugs authorized under exceptional circumstances are not usually expected to be in a position to provide the data package necessary for a full marketing authorization, though there have been some instances in the past where such drugs have been switched to a full marketing authorization.

Since 2006, 33 drugs have been approved under exceptional circumstances of which five have been withdrawn and another five have been granted full standard marketing authorization. The ones to receive a standard authorization are: Pandemrix, Focetria, Celvapan, Yondelis and Ilaris. "There are currently no corresponding generic medicinal products available [for these drugs]," the EMA clarified.

From the editors of Scrip Regulatory Affairs.
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Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Pfizer's *Mylotarg* (gemtuzumab ozogamicin) in combination therapy with daunorubicin and cytarabine for the treatment of adults with previously untreated, de novo acute myeloid leukemia	Oncologic Drugs	July 11
Novartis' tisagenlecleucel-T suspension for treatment of pediatric and young adults ages 3-25 years with relapsed/refractory B-cell acute lymphoblastic leukemia	Oncologic Drugs	July 12
Amgen's ABP 215, a proposed biosimilar to Genentech/Roche's *Avastin* (bevacizumab)	Oncologic Drugs	July 13 (morning)
Mylan's MYL-1401O, a proposed biosimilar to Genentech's *Herceptin* (trastuzumab)	Oncologic Drugs	July 13 (afternoon)
Intellipharmaceutics Corp.'s oxycodone extended-release tablets, with purported abuse-deterrent properties, for management of moderate-to-severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time	Anesthetic and Analgesic Drug Products/ Drug Safety and Risk Management	July 26
Safety and efficacy of Dynavax's hepatitis B vaccine	Vaccines and Related Biological Products	July 28
Janssen Biotech's *Plivensia* (sirukumab) for adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease-modifying anti-rheumatic drugs	Arthritis	Aug. 2

Pink Sheet

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