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Amsterdam 'Ticks Many Of Our Boxes,' Says EMA Head After Dutch Win Race To Host Agency

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Amsterdam is to be the new home of the European Medicines Agency after the Dutch capital beat the northern Italian city of Milan in a nailbiting voting process that was eventually decided by the drawing of lots.

Three cities – Amsterdam, Copenhagen and Milan – had made it through to the second round of voting, in which member state ministers gave Milan 12 votes, Amsterdam nine, and Copenhagen just five, putting the Danish capital out of the running.

The final result of the vote, which took place during the General Affairs Council in Brussels on Nov. 20, might have been different if Slovakia, which had put forward its capital Bratislava, had not abstained from voting after it failed to progress beyond round one. As it was, Amsterdam and Milan were tied in the final round and the winner was chosen by pulling the name out of a bowl.

Reaction to the result was predictably mixed. Many welcomed the choice of Amsterdam – the EMA's executive director Guido Rasi remarked that it "ticks many of our boxes" and said a joint governance structure would be set up to oversee the relocation project. Gerard Schouw, director of the Dutch Innovative Medicines Association, said it was "great news" that the EMA was coming to Amsterdam, and that it would "provide an enormous boost to the R&D activities of the sector and thus put our country on the map as a global player in the field of innovation." But others bemoaned the fact that a momentous decision such as the future location of a major EU agency should have been taken on what amounted to a coin toss.

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> Milan "was defeated only because of the drawing of lots and bad luck" – Massimo Scaccabarozzi, head of Italian industry body Farmindustria

Italy was bitterly disappointed, given that up to that point Milan had been ahead in the voting. Massimo Scaccabarozzi, president of the Italian pharmaceutical industry association Farmindustria, said: "We won all the same. Italy showed that

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EMA Relocation: EU Approval Delays Cannot Be Ruled Out

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Now that the European Medicines Agency knows where it is going after Brexit, the business of preparing for the move can begin. Being able to ensure business continuity during and after the relocation will be highly dependent on the EMA's ability to retain as many of its current staff as possible. Job losses are expected but it could be some time before it's clear which business operations will be affected.

CMS Efforts On Value-Based Payments Should Focus On Removing Barriers, PhRMA Says

https://pink.pharmaintelligence.informa.com/PS122007

The Pharmaceutical Research and Manufacturers of America says the US Centers for Medicare and Medicaid Services should not itself initiate experiments with value-based payment approaches. Any demonstrations led by agency's CMMI should focus on "holistic" approaches to health costs.

Generic Abuse-Deterrent Opioids: Comparison To Brand Will Not Require Use Of Control

https://pink.pharmaintelligence.informa.com/PS122008

FDA final guidance recommends comparative pharmacodynamic studies for nasal and oral routes of abuse, simplifies statistical approach to show deterrence of generic is same as brand.

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it could reach the highest level of the podium on an assessment of its merits. In the first voting rounds Italy in fact obtained more votes than the other candidates. This demonstrates that Milan best matched the quality characteristics that were requested. And it was defeated only because of the drawing of lots and bad luck."

Copenhagen will also have felt the pain, having invested a lot of effort in a lengthy, high-profile lobbying and publicity campaign. Lars Rebien Sørensen, who spearheaded Denmark's efforts to secure the EMA, was generous in defeat, thanking all those who supported the bid and tweeting "big congratulations to Amsterdam… Good choice that will ensure business continuity of EMA to the benefit of all Europeans!"

LONDON THE REAL LOSER

But many would say that the real loser is London, which has hosted the EMA since its creation in 1995 and is now seeing it taken away as a direct result of the UK's decision to leave the EU. Moreover, the capital is also losing another EU agency – the European Banking Authority, which is to move to the French capital Paris after a separate vote in Brussels that also ended in the drawing of lots.

The European Commission said that the relocation of the two agencies was "a direct consequence – and the first visible result – of the United Kingdom's decision to leave the European Union." It added that the EMA and the EBA were "two key regulatory agencies for the EU's Single Market, and are essential for the authorisation of medicines and for bank regulation. They must continue to function smoothly and without disruption beyond March 2019."

Following the EMA decision, Steve Bates, CEO of the BioIndustry Association, said: "London's loss is Amsterdam's gain. Today's decision on the location of the European Medicines Agency means 1000 high quality jobs leaving the UK, disrupting 1000 families as a direct result of Brexit, with implications for thousands more."

Winning the EMA is a massive deal for Amsterdam, not only because of the prestige of hosting a very highly regarded agency but because of the practical benefits it brings, such as synergies with local regulators, the biopharmaceutical industry and the research community, and the fact that tens of thousands of experts visit the EMA every year, with obvious knock-on benefits for the local economy.

> "Amsterdam ticks many of our boxes. It offers excellent connectivity and a building that can be shaped according to our needs"
> – EMA director Guido Rasi

The EMA itself was clearly relieved by the decision, having feared that it could end up in a city where its many of its staff might not want to live. Rasi said: "We welcome today's decision on the new location of EMA. Now that we finally know where our journey is taking us, we can take concrete actions for a successful move." He added that "Amsterdam ticks many of our boxes. It offers excellent connectivity and a building that can be shaped according to our needs. I am very grateful that the Member States took into account our requirements for business continuity and gave priority to the protection of public and animal health."

DISRUPTION MINIMIZED?

The relocation will inevitably result in disruption to the EMA's activities. The big question is to what degree. Staff retention – which had been a key concern at the agency – is expected to be pretty high, if the results of an EMA staff survey earlier this year are anything to go by. The survey put Amsterdam among the employees' preferred host cities, alongside Barcelona, Copenhagen, Milan and Vienna. *(Also see "EMA Discloses Staff's Preferred Host Cities, Amid Fears Relocation Could Batter Its Budget" - Pink Sheet, 9 Oct, 2017.)*

"Our internal surveys have shown that a large majority of EMA staff would be willing to move with the Agency to Amsterdam," Rasi declared. "However, even in this case, our activities will be impacted and we need to plan for this now to avoid the creation of gaps in knowledge and expertise."

Ensuring business continuity and medicines supply as far as possible during and after the relocation has been a concern not only for the EMA but for the pharmaceutical industry and the wider life science sector, which also want to see some sort of collaborative arrangements between the UK and the EU regulatory network after Brexit.

"Businesses now need certainty," declared BIA chief executive Bates. The best way to provide that certainty, he said, was "by an early agreement to a transition timeframe and continued close regulatory co-operation. We must now ensure Brexit does not disrupt the safe supply of vital medicines to tens of millions of families in the EU 27 and the UK."

LONG ROAD AHEAD

The EMA and the EU institutions now face the lengthy and challenging process of readying the new premises for the EMA to occupy before the Brexit date of March 29, 2019. Helping staff relocate to the Amsterdam area and settle in will be a key part of the project.

The EMA said the decision on the new location marked the "official start of a challenging joint relocation project that will have to be delivered within extremely tight timelines whereby the relocation has to be completed by 30 March 2019." Effective collaboration between EMA and the Netherlands on the basis of the commitments made in its offer to host EMA was "essential to ensure a successful move and the continuation of EMA's operations with minimal disruption."

The EMA and the Netherlands will kick start their collaboration by establishing a joint governance structure to steer and oversee the relocation project, it declared. "Because of its important role to safeguard public and animal health in the EU, EMA is committed to giving stakeholders and the public full visibility of the relocation project. In early December, the Agency will make available a monitoring chart on its website that will allow to track the progress made."

UK EFFECTS

There are also the effects on the UK and the Medicines and Healthcare products Regulatory Agency to consider, given the key role that the MHRA has played in the EMA and the wider EU regulatory network over the past couple of decades.

Sarah Haywood, CEO of MedCity, the life sciences cluster organization for London and the Greater South East, said that while it was disappointing that EMA was moving to Amsterdam after 22 years in London, "we must recognise the important role our domestic regulator, the MHRA, makes and will continue to make to enable access to new medicines and products."

Haywood said it was important to focus on "limiting the impact of the relocation by ensuring our regulation system is aligned with the EU, and we are working with the Mayor of London to reduce any disruption for researchers and companies, and, ultimately, patients." With more than 1,300 life sciences companies, world-class teaching hospitals, a strong pharma pipeline, and two of the world's top 10 universities, "I am confident that London will continue to thrive as a centre of research and innovation," she declared.

The EMA is already in the process of reassigning UK regulatory work to other EU member states as part of the Brexit process.

By the editors of Scrip Regulatory Affairs. Published online November 21, 2017

GENERIC DRUGS

FDA Contradicts AAM's Generic Market Consolidation Argument

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FDA may wind up hurting the generic industry's drug pricing narrative that deflation could force market consolidation and ultimately drug shortages.

Whether or not it was an off-the-cuff quip, Office of Generic Drugs Director Kathleen Uhl seemed to de-escalate the crisis that AAM President and CEO Chip Davis has warned on multiple occasions is coming absent changes.

During remarks to open the recent AAM Fall Tech Conference, Davis reiterated to the audience that generics are subject to a different set of economic levers than brand medicines. Generics function in a more commodity-style environment, while brand drugs rely on formulary management and reimbursement, he said.

Davis then warned that the market eventually could shrink because more than 200 generic manufacturers are forced to sell to three buying consortia that control 90% of wholesale purchases in the US.

"We are at an unprecedented level of deflationary pricing here in the US for generic drugs," Davis said.

"As these purchasers move more and more toward a single source contract for generic drugs, it creates a dynamic where it is entirely conceivable that no more than three generic manufacturers may be able to successfully market any given product.

> "Irregardless of what Chip just said about competitiveness with only three vehicles to get stuff to market, we in the generic drug space in the agency are seeing no signs of anything slowing down whatsoever in generic drug development, generic applications to the agency." – FDA's Uhl

This dynamic risks future competitive success in the generic market as our companies may be forced to maximize economies of scale and consolidate themselves or in some cases discontinue some products, which could lead to an increased risk of drug shortages and overall as a market higher, not lower, prices."

Margins and growth are expected to be limited in the coming years, which is pressuring generics companies.

Davis has made that argument in favor of legislation supporting access to generics, including bills combating abuse of the Risk Evaluation and Mitigation Strategy system and other moves by brand companies to prevent generic competition. There are numerous efforts underway to try and end them, including some by FDA. *(Also see "Q&A With US FDA Commissioner Scott Gottlieb" - Pink Sheet, 9 Nov, 2017.)*

FTC also recently conducted a workshop on generic market competitiveness. *(Also see "Beyond Pay-For-Delay: US FTC Digs Deeper On Barriers To Generic Competition" - Pink Sheet, 9 Nov, 2017.)*

The surprise came about 25 minutes later when Uhl presented on the state of OGD.

Uhl said when GDUFA I ended, there were more applications, amendments and controlled correspondence than were expected, and that all signs point away from Davis' prediction.

"The number of companies in the generic space is increasing," she said. "Every day I'm seeing emails come across on my inbox and they're companies I never heard of and they're potentially even getting ANDA ap-

provals. So there's new companies in this space and there are new facilities.

"Irregardless of what Chip just said about competitiveness with only three vehicles to get stuff to market, we in the generic drug space in the agency are seeing no signs of anything slowing down whatsoever in generic drug development, generic applications to the agency."

Indeed, several changes were made for GDUFA II to help more manufactures enter the market, including changes to the user fee structure to help small businesses. *(Also see "Generic User Fee 'Relief' For Small Firms Would Mean Bigger Bills For Large One" - Pink Sheet, 25 Jan, 2016.)*

APPROVAL VOLUME STARTS GDUFA II STRONG

FDA began GDUFA II with a near record for approvals, posting 87 in October.

It was the second-highest monthly total posted since the GDUFA era began in October 2012. In June, the agency reported 88 approvals (*see chart below*). *(Also see "ANDA Approvals Break Record, May Set New Normal" - Pink Sheet, 10 Jul, 2017.)*

At the same time, the agency gained a break on the number of ANDAs submitted. Only 65 were sent to the agency in October, according to FDA data. The total is more than 40 less than the FY 2017 monthly average.

It was thought that the increase in ANDA user fees might cause sponsors to rush to send applications to FDA before the end of the previous user fee regime. *(Also see "There's The Bolus! ANDA Sponsors Race To Avoid User Fee Spike" - Pink Sheet, 9 Oct, 2017.)*

SUBMIT EARLY IN THE MONTH, AVOID THE BOLUS

FDA also indicated that early in the month may be a better time to send an ANDA to the agency, as opposed to the end.

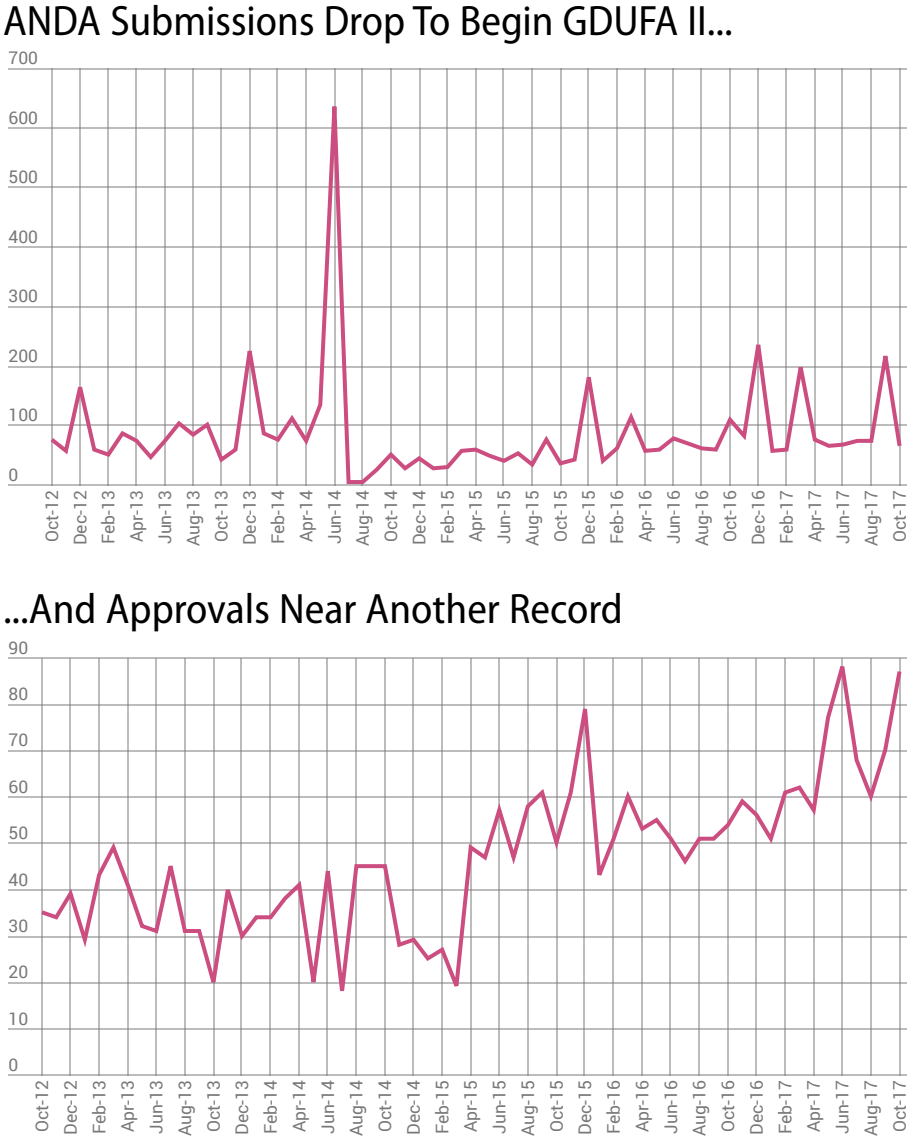
Ted Sherwood, director of OGD's Office of Regulatory Operations, said during the conference that the last application bolus – 216 ANDAs sent in September – included 100 applications submitted on Sept. 30. It was the day before fees increased 144%. *(Also see "Generic User Fee Hikes Could Disrupt US FDA Drug Pricing Campaign" - Pink Sheet, 28 Aug, 2017.)*

Sherwood said submitting that many ANDAs on a single day is "a lot for us to digest" and suggested sponsors think about sending applications early in a month if they are prepared.

"If you're ready, let it go," he said. "The earlier in the month you submit, you get ahead slightly of these sort of boluses of applications."

Indeed, FY 2017 was characterized in part by several dramatic spikes in ANDA submissions. *(Also see "Generic Drug Puzzle: Why Did ANDA Submissions Spike Again?" - Pink Sheet, 11 Apr, 2017.)*

FDA has said that the inconsistent submission volume makes workload planning and management difficult. The agency underestimated the number of applications expected each year in GDUFA I and thus staffing levels were not adequate to meet the demand. *(Also see "GDUFA: FDA Struggles Under Higher-Than-Expected Submission Volume" - Pink Sheet, 3 Mar, 2014.)*



GDUFA II began with a another boost for generic drug approvals, finishing one less than the highest monthly total since the user fee program launched. At the same time, submissions dropped, likely because ANDA user fees increased substantially.

Source: FDA generic drug program activity report

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AAM, PhRMA Renew Rivalry In Hatch-Waxman Public Comments

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In what has been a busy year of innovators and generic companies sparring over how to foster a more competitive marketplace, the Association for Accessible Medicines (AAM) and the Pharmaceutical Research and Manufacturers of America (PhRMA) renewed their rivalry on the issue in comments to the US FDA.

The groups submitted recommendations to an FDA docket opened in connection with the agency's July public meeting on administering the Hatch-Waxman Amendments to ensure a balance between innovation and access. *(Also see "Brands Push Back Against REMS Reform, Call Problem Small With Burdensome Fixes" - Pink Sheet, 18 Jul, 2017.)*

AAM submitted a 38-page comment to the docket with a mix of general and specific recommendations to improve access to generic drugs, while PhRMA refuted claims it is misusing the system to delay generic entry.

One of AAM's most notable recommendations was for FDA to take enforcement actions within its existing statutory authority against brand drug makers who fail to turn samples of a drug with a Risk Evaluation and Mitigation Strategy (REMS) over to a generic firm for bioequivalence testing.

Specifically, AAM requests FDA to include a statement in all REMS "that if a brand company fails to provide a generic applicant with the requested drug product in a timely manner (e.g., within 30 days of receiving a request), FDA will consider such failure to be a 'use' of a REMS to block or delay generic competition in violation of section 505-1(f)(8) of the FDC Act and that the sponsor may be subject to immediate enforcement action."

The generic drug trade association argues that by failing to comply with a REMS requirement, the innovator drug is rendered misbranded.

AAM says the Federal Food, Drug and Cosmetic Act provides for certain criminal and civil penalties against sponsors who commit a prohibited act, including seizure, injunction, criminal fines and imprisonment. However, the group notes that FDA has not yet acted against companies who misuse REMS.

"Although FDA has acknowledged the statutory authorities under the FDC Act to address REMS abuses by brand companies, FDA has not brought an enforcement action against brand companies that have manipulated REMS requirements to block or delay generic competition," AAM says. "As a result, brand manufacturers continue to engage in anti-competitive practices using REMS with little fear of reprisal."

Nevertheless, AAM contends that FDA's current statutory authorities are insufficient to address REMS abuse. CEO Chip Davis renewed his call for Congress to pass the CREATES Act and the FAST Generics Act. *(Also see "REMS Could Block ANDAs With 'Legitimate Business Justification' In Senate Bill" - Pink Sheet, 30 Apr, 2017.)*

Under FDA's existing authorities, "there remains a risk that such penalties pale in comparison to the financial rewards of such practices and that the penalties may be seen as merely the 'cost of doing business,'" Davis says.

The group also requests that FDA condition the approval of a REMS on the brand drug maker's agreement to enter into a shared system REMS with potential generic applicants.

CITIZEN PETITION ASSESSMENTS

AAM additionally outlined a proposal to address 505(q) citizen petitions that seek to delay the approval of a competing product. It specifically recommended FDA conduct a 30-day pre-filing citizen petition assessment "to determine the substantial completeness of a 505(q) citizen petition to warrant a full review," akin to the Office of Generic Drugs determining whether an abbreviated new drug application (ANDA) is substantially complete to permit a full review.

"If FDA determines after the 30-day pre-filing assessment is completed that the citizen petition lacks sufficient merit to warrant a substantive review, then FDA should deny the petition," AAM writes. "While the petition may be resubmitted with additional information, a pre-assessment should weed out meritless petitions and decrease the amount of time that approval of an ANDA can be potentially delayed."

FDA GRANTS ORANGE BOOK WISH

An additional item on AAM's wish list was for FDA to include a new column in the Orange Book titled "Patent and Exclusivity List" that identifies the date that a particular patent was considered listed in the Orange Book.

The agency announced Nov. 21 that search results and drug

PhRMA contended that REMS with Elements To Assure Safe Use (ETASU) do not upset Hatch-Waxman's intended balance of access and innovation, noting that of the 44 REMS with ETASU programs, 10 have a single shared system, "meaning that generic versions have been approved."

listings in the Orange Book now show patent submission dates where available.

"The FDA is publishing this data to improve transparency and provide additional information to regulated industry and the public," the agency said. "This information may help generic drug manufacturers determine the earliest date when they may be able to market new generic medicines."

FDA noted that the change also reflects a commitment in the October 2016 final rule "Abbreviated New Drug Applications and 505(b)(2) Applications."

PHRMA CLAWS BACK

While both the public meeting and comment docket were dominated by voices from those advocating improved generic access, brand drug makers spoke out in their defense.

PhRMA responded with a 23-page comment of its own, much of which responded to charges made against it on issues such as REMS misuse, citizen petition delay tactics and product hopping.

The pharma trade group contended that REMS with Elements To Assure Safe Use (ETASU) do not upset Hatch-Waxman's intended balance of access and innovation, noting that of the 44 REMS with ETASU programs, 10 have a single shared system, "meaning that generic versions have been approved."

University of Missouri School of Law professor Erika Lietzan echoed PhRMA's sentiment in her comments. She said there are only 22 brand drugs that have access restrictions where an ANDA has not been filed, and that more than half of those drugs still have data exclusivity, meaning there cannot be an approved generic or biosimilar anyway. *(Also see "Pay-For-Delay, REMS Reform Legislation Making (Slow) Progress In House" - Pink Sheet, 27 Jul, 2017.)*

AAM nevertheless contends that there is growing room for REMS abuse, writing that FDA is increasingly requiring new drugs to be approved with REMS with ETASU.

On citizen petitions, PhRMA sought to discredit claims that all innovator citizen petitions lack merit. The allegations, PhRMA said, "are based on flawed metrics and incomplete analysis."

"Relying upon data purportedly showing that FDA denies a high percentage of innovator citizen petitions, some observers claim that innovators file frivolous petitions to delay generic entry," PhRMA wrote. "The underlying studies did not attempt to assess the strength of these petitions on the merits, however. Further, these claims are based on data that count only the raw number of petitions denied—including petitions that FDA denied without comment on their merits."

PhRMA also pointed to FDA's data, which says only 4% of petitions received by the agency between fiscal years 2008 through 2015 resulted in the delay of an ANDA approval. *(Also see "Citizen Petitions Targeting ANDAs Recede, But Concerns Over Resources Remain" - Pink Sheet, 19 Aug, 2016.)*

The trade group also refuted claims of anticompetitive product hopping, writing that post approval changes to products " are a critical part of pharmaceutical innovation and the Hatch-Waxman balance, producing important treatment benefits for patients and advancing the standard of care."

This defense comes amid several proposals to raise the bar for approvals that involve only a slight reformulation. *(Also see "Brand 'Evergreening' Piques FDA Interest, But Solutions Remain Elusive" - Pink Sheet, 19 Jul, 2017.)*

"As a legal matter, there is no basis in the [Federal Food, Drug, and Cosmetic Act] for FDA to apply a different approval standard for original NDAs for new active ingredients, on the one hand, and modifications to previously-approved active ingredients submitted via a supplemental NDA or new NDA, on the other," PhRMA wrote. "The statute has one approval standard for NDAs and sNDAs."

The Biotechnology Innovation Organization (BIO) offered similar defenses of innovators in its own comments.

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100% User Fees: A 'Bad Idea' That May Be Inevitable

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"Bad idea." That is how Amgen SVP-Global Regulatory Affairs & Safety Steven Galson characterized the Trump Administration proposal to increase user fees to cover the full cost of product reviews. Galson, the former head of the US FDA's Center for Drug Evaluation & Research, was asked about the proposal during the Prevision Policy/Friends of Cancer Research Biopharma Congress Nov. 14.

President Trump called for a doubling of user fees to fully fund reviews in his budget request for fiscal 2018; it was not enacted as part of the user fee reauthorization this year, but it could re-emerge in future appropriations bills.

Galson made very clear that he doesn't like the idea. "The public needs some ownership of what is going on," he said. The current model "achieves some important celestial balance that's working at FDA. I just don't think that's wise public policy."

Other industry panelists agreed. "It's not the money," Merck SVP-Global Regulatory Affairs and Clinical Safety Sandra Milligan said. "It's the balance."

Having industry fully fund reviews would only fuel the perception of conflicts of interest, she said. "It would certainly be a stronger lightening rod I think for public opinion if it was 100% funded by us. I don't think we could do anything right at that point."

But don't look for the Trump Administration to drop the idea – and, for that matter, don't assume that it won't happen no matter who is running the negotiations for the next user fee reauthorization in 2022.

Office of Management & Budget Associate Director for Health Programs Joe Grogan made clear during his remarks at the Biopharma Congress that Trump isn't likely to drop the idea, describing it as an example of the President's willingness to take on "sacred cows."

Grogan described the goal as driven by budgetary necessity. "We're out of money. We're spending a ton of money that we don't have every year," he said. "We have to look to places maybe that we don't want to, to find money." The President "wanted to spark a debate about should premarket review be funded by industry completely," Grogan said. "It wasn't all the safety functions and it wasn't the entire agency. It was this particular function of it.

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"Having industry fully fund reviews would only fuel the perception of conflicts of interest, Merck's Milligan said. "It would certainly be a stronger lightening rod I think for public opinion if it was 100% funded by us. I don't think we could do anything right at that point."

Moreover, Grogan argued, the trend in user fees makes it all but inevitable that industry will end up paying the full cost of reviews. "Look at the trend line. We're at like 72% now," he said. "I guarantee it goes up and four and a half years from now we'll be above where we are now. I think it's a debate we should have about the level of taxpayer support for the review process."

Grogan made clear that the White House is happy with the user fee reauthorization as it stands. "Congress made a decision to pass a clean PDUFA. I think it's a great PDUFA package, probably the best one I've ever seen, and industry and FDA should be congratulated on it." That said, "I do think we need to talk about the level of industry support for FDA."

From the editors of the RPM Report. Published online November 20, 2017

Medicare May Require Part D Plans To Provide Point-of-Sale Rebates

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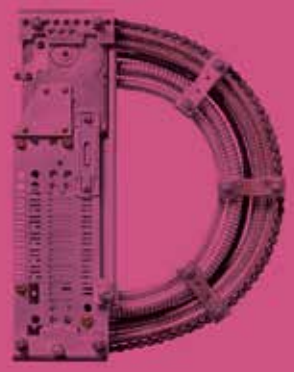
The Centers for Medicare and Medicaid Services is considering requiring Medicare Part D plans to apply at least a percentage of manufacturer rebates to reducing beneficiary cost sharing at the point of sale and is seeking stakeholder input on the change.

A "request for information" on redirecting Part D rebates and pharmacy price concessions is part of a proposed rule on Medicare Advantage and Part D policy and technical changes for 2019. The proposal is scheduled to be published in the Federal Register Nov. 28. Comments are due by Jan. 16.

The proposal is the third Medicare regulation addressing drug pricing to be released recently by the Trump Administration. Like the other two, this one does not directly target manufacturers' ability to set prices. Instead, the latest proposal adopts biopharma's argument that pharmacy benefit managers and plans should lower drug costs for seniors by changing the way they handle rebates. *(Also see "Medicare Part D Rebate Pass-Throughs To Beneficiaries Is 'On The Table'" - Pink Sheet, 26 Jul, 2017.)*



"We believe such an approach could reduce the incentive for sponsors to favor high-cost/highly-rebated drugs [over] lower net cost alternatives..."

"In this request for information we discuss considerations related to, and solicit comment on, requiring sponsors to include at least a minimum percentage of manufacturers rebates … in the drug's negotiated price at the point of sale," the proposed rule says.

The agency is interested in ways to implement point-of-sale rebates without increasing government costs and without reducing manufacturer payments under the coverage gap discount program. Feedback will be used for "consideration of future rulemaking on this topic."

Currently Part D sponsors are allowed, but not required, to apply rebates and other price concessions at the point of sale to lower the price and beneficiary cost sharing. However, sponsors have elected to do so only "rarely," CMS notes.

Instead, price concessions are generally reported by plans at the end of the year as "direct and indirect remuneration" (DIR) and are used by CMS to calculate final plan payments. The practice leads to price concessions reducing plan premiums and the government's subsidies of those premiums – and to increasing plan profits, CMS notes.

Sponsors "sometimes opt for higher negotiated prices in exchange for higher DIR and, in some cases, even prefer a higher net cost drug over a cheaper alternative," CMS says. "This may put upward pressure on Part D program costs and … shift costs from the Part D sponsor to beneficiaries, who utilize drugs in the form of higher cost-sharing, and to the government, through higher reinsurance and low income cost-sharing subsidies."

Beneficiary cost-sharing amounts are based on the price of the drug before rebates are applied, which means "higher overall out-of-pocket costs, even after accounting for the premium savings tied to higher DIR," CMS maintains.

PORTION OF REDIRECTED REBATES WOULD REFLECT AVERAGE IN CATEGORY OR CLASS

CMS lays out a number of specifics on how the new approach would work. The agency is considering requiring Part D sponsors to include in negotiated drug prices a specified minimum percentage of the cost-weighted average of rebates provided for drugs in same therapeutic category or class. Calculating an average at the category/class level would help maintain the confidentiality of the manufacturer-payer relationship, the agency explains.

CMS also invites comment on whether a more limited version of the plan should be considered, such as one targeting only certain drugs that most directly contribute to increasing Part D costs in the catastrophic phase of the benefit or those with high-price/high-rebate arrangements.

The proposal does not offer a specific percentage that would be applied but envisions that it would be below 100% of the rebate. CMS is also thinking about using the same percentage for all drugs. In the proposal, the agency modeled the cost impact of point-of-sale rebates over 10 years using percentages ranging from 33% to 100%. (*See box.*)

CMS said it is aware that requiring point-of-sale rebates will reduce cost sharing for "many" beneficiaries but at the same time will result in larger premiums for all beneficiaries. *(Also see "Medicare Part D Premiums Dip As Rebates Grow Faster Than Drug Costs To Plans" - Pink Sheet, 3 Aug, 2017.)*

As a result, "we aim to set the minimum percentage of rebates

that must be applied at the point of sale at a point that allows an appropriate balance between these outcomes and thus achieves the greatest possible increase in beneficiary access to affordable drugs."

In its modeling, CMS found point-of-sale rebates result in a net reduction in beneficiary costs (including cost-sharing and premiums) ranging from $19.6bn to $56.9bn over 10 years, depending on the portion of rebates that is redirected. At the same time, government costs could increase from $27.3bn to $82.1bn.

> While CMS modeling found point-of-sale rebates result in a net reduction in beneficiary costs, government costs could increase from $27.3bn to $82.1bn over 10 years.

However, the model does not take into account possible changes in behavior related to drug pricing that would further reduce Part D costs for beneficiaries and the government. For example, "we believe such an approach could reduce the incentive for sponsors to favor high-cost/highly-rebated drugs [over] lower net cost alternatives…and also potentially increase the incentives for sponsors and PBMs to negotiate lower prices at the point of sale instead of higher DIR."

The agency seeks comment on a number of other components of the methodology for implementing point-of-sale rebates, including:

- Rebate amounts would be based on expected rebates for the current year, not historical amounts.
- Average rebate amounts would be calculated using only drugs that are rebated.
- Each drug with a unique 11-digit national drug code will be considered separately for calculating the average rebate amount.
- Average rebate amounts would be calculated separately for each plan.
- When calculating the average rebate, the rebate amount for each drug in a category would be weighted by the total gross costs incurred for each drug over the most recent period for which data is available.
- Plan sponsors would recalculate the average rebate amount periodically.
- Average rebate calculations would be made by plan sponsors with attestations about their accuracy.

PBMS, PLANS DISAGREE WITH PREMISE

The Pharmaceutical Care Management Association challenged the point-of-sale rebate idea, noting in a release it would "raise premiums by up to $28 billion and taxpayer costs by up to $82 billion over the next decade." Such a requirement "would also create a windfall for drugmakers, who would pay up to $29 billion less in donut-hole discounts," the group said.

PCMA expressed relief that the proposal only invited comments on the point-of-sale rebate idea and did not present it as a requirement.

"Notably, the proposed rule addresses both the point-of-sale rebates and direct and indirect remuneration (DIR) issues through a request for information (RFI) rather than a requirement," the group commented. "We are also encouraged CMS continues to allow plan sponsors the option to use the price concessions they negotiate with manufacturers and drugstores to reduce premiums and other costs."

A spokesperson for America's Health Insurance Plans said in an email that "rebates are already returned to Americans who have a Part D plan in the form of lower premiums and other costs. Drug prices are set by the pharmaceutical companies who manufacture them. The best way to make prescriptions more affordable is to price them more reasonably from the very start."

Published online November 17, 2017

Impact of Point-of-Sale Rebates In Medicare Part D, 2019 through 2028

COSTS	33% OF REBATES	66% OF REBATES	90% OF REBATES	100% OF REBATES
Beneficiary Cost-Sharing	-$28.8bn	-$57.8bn	-$78.9bn	-$85.2bn
Beneficiary Premiums	$9.2bn	$18.7bn	$25.7bn	$28.3bn
Beneficiary Net	-$19.6bn	-$39.1bn	-$53.2bn	-$56.9bn
Government Costs	$27.3bn	$55.1bn	$75.5bn	$82.1bn
Manufacturer Gap Discount	-$9.7bn	-$19.4bn	-$26.4bn	-$29.4bn

Source: CMS Proposed Rule on Medicare Advantage and Medicare Part D

Part D Proposal Aims To Promote Biosimilars, Generics To Reduce Costs

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The US Centers for Medicare and Medicaid Services is proposing formulary and cost sharing changes in Medicare Part D aimed at promoting use of biosimilars and generic drugs and lowering beneficiary and government spending.

The changes are part of a broad proposed rule scheduled to be published in the Nov. 28 Federal Register that lays out a wide range of policy and technical changes in Medicare Advantage, Medicare Part D and other programs for 2019. Also among them is the possible requirement that Part D plans must apply a portion of drug rebates to reduce beneficiary cost sharing at the point-of-sale. *(Also see "Medicare May Require Part D Plans To Provide Point-of-Sale Rebates" - Pink Sheet, 17 Nov, 2017.)*

For biosimilars, the agency has decided to require that cost sharing be reduced to the level of generic drugs for all beneficiaries qualifying the Part D low income subsidy (LIS) as well as for non-LIS beneficiaries who have reached the catastrophic level of the benefit. Those beneficiaries are currently subject to brand-level cost sharing for biosimilars.

> For biosimilars, CMS will require that cost sharing be reduced to the level of generic drugs for all beneficiaries qualifying the Part D low income subsidy (LIS) as well as for non-LIS beneficiaries who have reached the catastrophic level of the benefit.

The decision reflects a concern with fostering the biosimilar market and is consistent with an earlier CMS decision to reimburse biosimilars under Medicare Part B in a way that offers incentives for the development of biosimilar competitors referencing the same innovator. *(Also see "Biosimilar Coding Policy For Medicare Reversed To 'Promote Innovation'" - Pink Sheet, 3 Nov, 2017.)*

"Treatment of follow-on biological products, which are generally high-cost, specialty drugs, as brands for the purposes of non-LIS catastrophic and LIS cost sharing generated a great deal of confusion and concern for plans and advocates alike, and CMS received numerous requests to redefine generic drugs" to include biosimilars with respect to cost sharing for those beneficiaries, the agency says.

"We agree and propose to revise the definition of generic drug … to include follow-on biological products … solely for purposes of cost sharing" for those two groups of beneficiaries. "Lower cost sharing for lower cost alternatives will improve enrollee incentives to choose follow-on biological products over more expensive reference biological products, and will reduce costs to both Part D enrollees and the Part D program."

Branded drug cost sharing for LIS beneficiaries currently ranges from $3.70 for those below the federal poverty level to $8.25 for those above the poverty threshold. Copays for generics ranges from $1.20 to $3.30 for LIS beneficiaries.

Most non-LIS beneficiaries are responsible for 5% coinsurance for brands and generics when they reach catastrophic coverage. Members progress to the catastrophic phase of the Part D benefit after logging $7,425 in total drug costs, including both beneficiary and Medicare spending.

With the growing number of very high cost drugs on the market, Part D beneficiaries are progressing more quickly to the catastrophic phase and a 5% co-

insurance can be a significant financial burden because it is a percentage of the drug's price before rebates.

CMS cautions that it would only consider biosimilars as generics for the purposes of non-LIS catastrophic and LIS cost sharing and not for other types of formulary policies.

The agency "currently considers biosimilar biological products more like brand name drugs for purposes of transition or mid-year formulary changes because they are not interchangeable," it explains. "In these contexts, treating biosimilar biological products the same as generic drugs would incorrectly signal that CMS has deemed biosimilar biological products (as differentiated from interchangeable biological products) to be therapeutically equivalent."

> "CMS aims to revise and clarify the rules regarding requests for exceptions to formulary tiering, noting the increase in Part D formularies with five to six tiers.

IMMEDIATE GENERIC DRUG SUBSTITUTION

The proposal would also allow Part D plans more flexibility to implement generic substitutions without having to wait for clearance from CMS.

"Immediate generic substitution has long been an established bedrock of commercial insurance, and we are not aware of any harm to the insured resulting from such policies," according to the agency.

"Currently, Part D sponsors can add drugs to their formularies at any time; however, there is no guarantee that enrollees will switch from their brand name drugs to newly added generics. Therefore, Part D sponsors seeking to better manage the Part D benefit may choose to remove a brand name drug, or change its preferred or tiered cost-sharing, and substitute or add its therapeutic equivalent. But even this takes time."

To facilitate efforts to drive beneficiaries to generics, "we propose … to permit Part D sponsors to immediately remove, or change the preferred or tiered cost-sharing of, brand name drugs and substitute or add therapeutically equivalent generic drugs provided specified requirements are met," CMS says. They are that the:

Generic drug "would need to be offered at the same or a lower cost-sharing and with the same or less restrictive utilization management criteria originally applied to the brand name drugs;"

"Part D sponsor could not have as a matter of timing been able to previously request CMS approval of the change because the generic drug had not yet been released to the market;" and

"Part D sponsor must have previously provided prospective and current enrollees general notice that certain generic substitutions could occur without additional advance notice."

Under current regulations, Part D sponsors must submit formulary change requests to CMS and provide specified notice before removing drugs or changing their cost-sharing, except for unsafe drugs or those withdrawn from the market. Plans must also provide 60-days' notice to enrollees and other specified entities in advance of the change.

EXCEPTIONS TO FORMULARY TIERING: STILL NOT FOR SPECIALTY DRUGS

The proposed rule aims to revise and clarify the rules regarding requests for exceptions to formulary tiering. The agency believes the issue needs to be addressed because of the increase in Part D formularies with five to six tiers, including two for generics (preferred and non-preferred) and tiers that mix brands and generics.

The exceptions process refers to situations where beneficiaries may request lower cost sharing for medically necessary drugs that plans have placed on high cost-sharing tiers.

CMS would revise current practice to prohibit plans from excluding non-preferred generic drug tiers from exceptions. The agency proposes to base eligibility for tiering exceptions on the tier that contains the preferred alternative drug to the higher-cost requested drug, rather than on tier labels applied by plans. So tiering exceptions for non-preferred generics would be assigned to the lowest applicable cost-sharing associated with either brand or generic drugs.

"Given the widespread use of multiple generic tiers on Part D formularies, and the inclusion of generic drugs on mixed, high-cost tiers, we believe these changes are needed to ensure that tiering exceptions for non-preferred generic drugs are available to enrollees with a demonstrated medical need," the proposal says.

Plans can continue to deny exceptions for drugs placed on the specialty tier, which are defined as those whose negotiated drug costs exceeds $670 per month. "We do not intend to change the criteria for the specialty tier, which has always been based on the drug costs," CMS says. "This proposal would retain the current regulatory provision that permits Part D plan sponsors to disallow tiering exceptions for any drug that is on the specialty tier."

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Ibrance v Kisqali: Quicker Novartis Discount Helps Cut UK NICE's Timeline

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NICE, the health technology appraisal institute for England and Wales, has recommended two breast cancer drugs for use on the National Health Service: Pfizer's *Ibrance* (palbociclib), and Novartis' *Kisqali* (ribociclib). While NICE took just 84 days to say yes to Kisqali, it took the best part of a year for the institute to issue positive recommendations on Ibrance. The difference in timelines could be down to the companies' willingness to compromise on price.

On Nov. 16, NICE published two pieces of final draft guidance, one for Novartis' Kisqali, which received EU approval in August 2017 and the other for Pfizer's Ibrance, approved in November 2016. Both are CDK4/6 inhibitors, a new class of drugs that mark "one of the most important breakthroughs for women with advanced breast cancer in the last two decades," according to the Institute of Cancer Research.

NICE found that both drugs stalled the growth of cancer for an average of an extra 10 months and described them as promising. The institute indicated that the recommendations were largely down to a reduction in price. "Discounts to the price of both of these promising new drugs mean they can be recommended as options for people with hormone receptor positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or secondary breast cancer, despite uncertainties about how long they extend overall survival," it said in a statement. However, the speed with which the two companies offered their discounts could be reflected in the speed with which NICE agreed to recommend them.

Excluding any discounts, Kisqali costs £2,950 for a 63-tablet pack of 200mg tablets, while Ibrance costs £2,950 for a 21-capsule pack of 125mg capsules.

Kisqali became the first drug to be recommended by NICE within 90 days under new arrangements for appraising cancer drugs that were introduced along with reforms to the Cancer Drug Fund. Now, NICE can start to review drugs before marketing authorization, and as Novartis points out, the first appraisal committee meeting can take place even before an opinion from the European Medicines Agency's scientific committee, the CHMP, has been issued. It took NICE just 84 days to make a positive recommendation.

But aside from the new process, Novartis says that "true collaboration" with the institute as soon as possible led to a NICE yes at the earliest possible opportunity. "We offered the NHS a good value option that addresses the needs of patients," said the firm. Indeed, early on in the process Novartis offered NICE a confidential discount as part of the patient access scheme. According to the final appraisal document, it was unclear whether the progression free survival benefits of Kisqali would lead to a survival benefit. "But with the patient access scheme discount, ribociclib is a cost-effective use of NHS resources and it can be recommended," said the final appraisal determination. It added that it was confident that cost-effectiveness estimates for the drug were in the range that the institute considers acceptable (between £20,000-£30,000 per quality adjusted life year.)

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> "We need NICE to work together with industry on a new process for evaluation where companies are encouraged to come forward with their best price much earlier in discussions. The current system is taking too long and prices still remain high,"
>
> – Paul Workman, Institute of Cancer Research

Meanwhile, Ibrance' road to a positive recommendation was "long and drawn out," according to Paul Workman, chief executive of the ICR. NICE held its first committee meeting in January 2017 and preliminary draft guidance followed in February. This stated that the cost of Ibrance was too high to justify its benefits, and in addition there were doubts about overall survival benefits. *(Also see "Pfizer To Compromise On NICE Price For Ibrance?" - Scrip, 2 Feb, 2017.)*

The appraisal was then paused while Pfizer put together an updated evidence package. It also provided the drug free of charge to all 800 eligible NHS patients until NICE and the Scottish Medi-

cines Consortium concluded their appraisals (an SMC decision is expected later this year.) According to the final appraisal document, the discount that Pfizer offered helped bring the incremental cost-effective ratios for Ibrance "within the range considered a cost-effective use of NHS resources."

Following the earlier negative recommendation, Pfizer commented that it had not initially offered a discount because meeting the £30,000 per QALY threshold would have meant a substantially lower price. "Under the current NICE methodology the monthly cost would have to be several hundred pounds per month (£293-£1,500), which is in the range of what chemotherapy was reimbursed at around 15 years ago," said Pfizer in February. The company had previously warned that offering discounts was not a sustainable way to secure access to medicines. *(Also see "Pfizer Laments Price Cut Needed To Secure Xalkori NICE Yes" - Scrip, 10 Nov, 2016.)*

Pfizer has long criticized the NICE appraisal system for cancer medicines, and has highlighted its problems with appraising add-on therapies. The company told the *Pink Sheet* that it discussed these challenges with NICE during the Ibrance appraisal process. "We are pleased that, in the case of palbociclib, NICE showed flexibility in enabling discussions to continue, meaning that we could go back with additional data and revisions to our economic case. Moving forward, we all need to continue working together to find ways of streamlining the process further."

The firm added that as cancer rates rise and advances in medicinal innovation are made, NICE's evaluation process for "pioneering" cancer treatments needs to be reformed. Pfizer said that an analysis that it commissioned showed that "UK patients are prescribed up to 75% less new medicines by volume per capita in the first year of launch compared to those in France, Germany, Japan, Switzerland and the US.".

In December 2015, Ibrance won a promising innovative medicine (PIM) designation from the UK regulator, the MHRA. A PIM designation is the first step in the MHRA's early access to medicines scheme (EAMS), which aims to give patients access to promising and innovative medicines that have not yet been approved. The PIM does not appear to have had much impact in getting Ibrance to patients earlier, although, Pfizer notes that the institute quoted the PIM designation in its final decision when discussing the innovative nature of the drug. "We are pleased NICE has recognized the MHRA's designation," it said.

Meanwhile, the ICR's Workman expressed frustration that NICE's recommendation for Ibrance took so long, even though Pfizer had provided it for free. "We need NICE to work together with industry on a new process for evaluation where companies are encouraged to come forward with their best price much earlier in discussions. The current system is taking too long and prices still remain high," he said.

From the editors of Scrip Regulatory Affairs. Published online November 17, 2017

FDA's NDA And BLA Approvals: Juluca

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				
Viiv Healthcare	Juluca (dolutegravir and rilpivirine)	Fixed-dose combination tablet of dolutegravir, a human immunodeficiency virus type 1 integrase strand transfer inhibitor (INSTI), and rilpivirine, a HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca.	P	11/21/2017

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

Lawsuit, Warning Letter Mark Return Of B. Cepacia As GMP Issue

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The return of *Burkholderia cepacia* contamination at two pharmaceutical manufacturing facilities, one of them blamed for the death of baby, serves as a reminder to monitor for and respond to any signs of the microorganism.

A wrongful death case from a 2016 outbreak and a new outbreak this year from the same source, PharmaTech LLC, of Davie, Florida, underscore the importance of ridding *B. cepacia* contamination from pharmaceutical manufacturing processes.

Meanwhile, a warning letter the US FDA recently sent a firm with recurring *B. cepacia* issues that led to four recalls over 10 years stresses the importance of properly monitoring for the microorganism. The firm, Sage Products Inc., Cary, Ill., was acquired by Stryker Corp. last year.

PHARMATECH, RUGBY LABS SUED OVER INFANT'S DEATH

An infant hospitalized at six months for a chronic lung disease died at nine months after she contracted a pulmonary *B. cepacia* infection, according to a complaint her family filed in July with a federal court in Pennsylvania against a contract manufacturer, PharmaTech LLC, of Davie, Florida, and an own-label distributor, The Harvard Drug Group LLC, doing business as Rugby Laboratories.

FDA had traced the 2016 outbreak to 10 lots of oral liquid docusate sodium laxative manufactured by PharmaTech for six distributors, including Rugby. FDA found *B. cepacia* in the water system PharmaTech used for manufacturing drug products. *(Also see "FDA Enforcement And Compliance In Brief" - Pink Sheet, 25 Oct, 2016.)*

During her hospitalization at the University of Pittsburgh Medical Center's Children's Hospital, the infant was regularly treated with Diocto Liquid docusate sodium from one of the contaminated lots, the complaint alleged.

The 2016 outbreak involved 63 confirmed and 45 suspected cases in 12 states. *(Also see "B. Cepacia Hits ICUs Again, Raises Manufacturing Controls Questions" - Pink Sheet, 6 Sep, 2016.)*

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Microscopic bacteria

This year's outbreak involves at least eight cases in two states. FDA also found bacteria, yeast and mold contaminants in recent tests of PharmaTech oral liquid docusate sodium samples that contain *B. cepacia*.

In August, PharmaTech, Rugby and two other distributors recalled all lots within expiry of all liquid products manufactured at PharmaTech's facility after learning from FDA of several adverse event reports of new *B. cepacia* infections possibly linked to docusate sodium solutions manufactured at PharmaTech.

Those events may have triggered the end of the company. PharmaTech's website is now offline, and the Sun Sentinel in Deerfield Beach, Florida, reports that the company has vacated its manufacturing plant.

SAGE PRODUCTS HIT WITH FDA WARNING LETTER

A July 17 FDA warning letter to Sage Products criticized the firm's approach to checking for objectional microorganisms like *B. cepacia*.

The warning letter also raised concerns about oversight of a contract manufacturer. *(Also see "FDA Offers Sage Advice On Contract Manufacturers: Don't Mix Drugs And Car Wax" - Pink Sheet, 30 Jul, 2017.)*

FDA said in the warning letter that the microbiological screening method Sage was using "has not consistently and reliably detected the presence of *B. cepacia* in your drugs before you released them for distribution."

The agency said that a better screening method would have avoided the need for recalls due to *B. cepacia* contamination of Comfort Shield 3% dimethicone cloths in 2006, 2% chlorhexidine gluconate cloths in 2008, Comfort Shield 3% dimethicone cloths in 2014, and of 3% dimethicone cloths, 2% chlorhexidine gluconate cloths, M-Care cleansing cloths and Comfort Bath cleansing wash cloths in 2016.

A root cause investigation after the most recent recall found a biofilm had become established in a clean-in-place system where *B. cepacia* also was identified.

FDA stressed in the warning letter that Sage's products "are often used in hospital or clinical settings in which patients may have a higher vulnerability to infection with *B. cepacia* and other objectionable organisms."

When Stryker Corp. announced its acquisition of Sage Products in February 2016, one of its group presidents called Sage "the market-leading company dedicated to the prevention of hospital-acquired conditions including pressure ulcers, surgical site infections, patient handling and ventilator-associated conditions." *(Also see "Stryker Sees Big Opportunity In Stopping "Never Events With $2.775b Sage buy" - Medtech Insight, 1 Feb, 2016.)*

The warning letter and subsequent recall of nearly 1.2 million cases of products that were either contaminated with *B. cepacia* or manufactured on the same lines as contaminated product signaled that Stryker also had acquired a potential source of dangerous hospital-acquired infections.

From the editors of the Gold Sheet.
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US FDA's Oncology Division Wants To Know About Your Pipeline, Not Just Your NDAs

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The US FDA's oncology review division is receiving previews of products in development from sponsors, in part so they can understand their goals beyond the next application.

Richard Pazdur, director of FDA's Oncology Center of Excellence, said the oncology review division is "inviting many of the companies in to present their pipelines."

For the agency, it appears to be a learning opportunity, rather than a chance to gain a head-start on a review. Pazdur said part of the idea is to help understand the drug sponsors' endgame, rather than simply work application to application.

"Where are they going with their molecules?" Pazdur said of the pipeline presentations Nov. 14 during the Biopharma Congress, sponsored by Prevision Policy and the Friends of Cancer Research. "And that's important for our reviewers to hear what they're ultimate game plan is rather than just getting an NDA or BLA dumped at your door so to speak."

"I know this is going to cause some heartburn in the industry, but we probably made a decision on your application before you even submitted it," Pazdur said.

At the same time, within the OCE, Pazdur is encouraging preclinical staff to discuss business and development practices with sponsors, such as "what are their molecules that they're looking at, what are their selection criteria for molecules going forward, why are they doing it, what are they looking at."

"It's probably aimed at an earlier interaction with industry than before," Pazdur added.

FDA also has established robust early interaction systems with sponsors of complex generics *(Also see "US FDA Commits To Meeting With Complex ANDA Sponsors, Works Hard To Avoid It" - Pink Sheet, 24 Oct, 2017.)* and biosimilars *(Also see "FDA Met Biosimilar Review Timelines But Missed Meeting Goals In 2015" - Pink Sheet, 25 Apr, 2016.)*.

ENGAGEMENT CRITICAL FOR SOME COMPANIES

Several sponsors apparently have taken advantage of the opportunity to discuss their early stage pipelines with the agency.

Merck & Co. Inc. said it has met with FDA on several occasions to provide "an overview" of its immune-oncology clinical development program. The company also told the Pink Sheet that it regularly communicates with the agency about the progress of clinical programs, "including plans for future trials as well as efficacy and safety updates from existing trials and anticipated submissions."

"This level of engagement is a critical component of our commitment to move as quickly as possible to bring new options to patients and ensure that our trials meet the highest scientific standards," a Merck spokesperson said.

Genentech Inc., which is part of **Roche**, also said that it has had

> "Where are they going with their molecules?" Pazdur said of the pipeline presentations Nov. 14.

"several conversations with the FDA on our pipeline across disease areas, as well as platforms."

A Genentech spokesperson would not comment on the details of the meetings, but said they have been worthwhile.

"We value the opportunity to discuss the breadth of our early-stage portfolio with regulatory officials," the company said.

The meetings, even if only to preview development that is years away from reaching the agency, could be an outgrowth of the success of FDA's breakthrough therapies program.

Breakthrough is built on the expectation that promising new drugs could gain an expedited path to market through early and frequent interaction with FDA officials. Hundreds of designations were issued during the program's first five years, many of which resulted in approvals, including several in the oncology space.

The program was so successful that stakeholders have argued that FDA should try to incorporate the lessons beyond program participants. *(Also see "PDUFA VII Already: Could Breakthrough Ideas Apply Outside Program?" - Pink Sheet, 26 Aug, 2016.)*

The idea also seems to fit with Pazdur's philosophy that his staff function more like an academic institution. He has said that reviewers in many ways discuss health problems just as an academic center. *(Also see "FDA Talent Hunt: Better To Recruit From Academia Than Industry?" - Pink Sheet, 14 Dec, 2015.)*

LAYING GROUNDWORK FOR FUTURE APPROVALS

Pipeline meetings also seem to feed into the Office of Hematology and Oncology Products' policy of encouraging senior leaders and rank-and-file reviewer discussions about applications and their associated issues.The Oncology Center of Excellence was created in part to encourage more collaboration among agency experts in the various product centers. *(Also see "FDA's Pazdur Jumps Over To New 'Moonshot' Role" - Pink Sheet, 29 Jun, 2016.)*

Pazdur said during the Friends of Cancer Research Annual Meeting on Nov. 15 that oncology reviewers often are discussing applications before they reach the agency, noting the policy is intended to help quality applications gain quicker approvals.

"I know this is going to cause some heartburn in the industry, but we probably made a decision on your application before you even submitted it," he said.

Published online November 20, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for drugs intended to treat interstitial cystitis and bladder pain syndrome; also, discussion of whether bladder pain syndrome and interstitial cystitis reflect overlapping or different populations, and whether it is appropriate to assess efficacy in the same way for both conditions	Bone, Reproductive and Urologic Drugs	Dec. 7
Clarus Therapeutics' 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. 9
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

Pink Sheet

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Phil Jarvis, Mike Ward

CORPORATE SALES
John Lucas, Elissa Langer

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Christopher Keeling

DESIGN
Jean Marie Smith

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Denise Peterson
Nielsen Hobbs
Mary Jo Laffler

Europe
Eleanor Malone
Maureen Kenny
Alex Shimmings

Asia
Ian Haydock

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