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Pink Sheet

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Novel Approvals Were Fewer But Faster At US FDA In 2016

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first cycle approval rates beget more high first cycle rates in a virtuous cycle; when there are fewer CRLs, there are fewer responses to CRLs.

Only one of the approvals in 2016, Shire PLC's dry eye drug *Xiidra* (lifitegrast), required two review cycles. As a result, 2016 had the highest first-cycle approval rate ever from the contemporary FDA: 95%.

The trend toward fewer complete response letters, however, came to a sharp halt in 2016. CDER issued more than a dozen CRLs to NMEs and novel biologic applications in 2016, decisions that could lead to more multiple-cycle approvals in future years.

VERY SHORT REVIEWS DRIVE DOWN AVERAGE TIME

The median time to approval for CDER novel agents in 2016 was 11 months, the same as both 2015 and 2014. However, 2015 and 2014, the average was higher than the median; a few long reviews pulled the average review time higher. Novel approvals in 2015 took an average of 15 months, and an average of 13.7 months in 2014.

In 2016, however, the average of 10 months was less than the median of 11 months, due to the preponderance of fast approvals and the corresponding lack of any long-review outliers. The longest time to approval for any 2016 NME/NBE was *Xiidra*, at 16.5 months – not much longer than the average time in 2015.

Six of the 2016 priority review drugs were approved in advance of the user fee

The average time from submission to approval for novel agents approved by FDA's Center for Drug Evaluation and Research in 2016 was only 10 months, the shortest average in the contemporary era.

But while speedy, the CDER class of 2016 is also unusually small. The final count of 22 novel approvals is the lowest annual total for the center since 2010, and is less than half of the almost two-decade high of 45 reached in 2015. (See pink.pharmamedtechbi.com for an interactive chart of CDER's 2016 novel approvals.)

The short average review time reflects the extremely high proportion of priority reviews among the approved products. More than two-thirds of the 2016 novel approvals received priority review, which comes with an eight-month review target (see graphic, p. 4).

The short average review time is also partly the culmination of the declining numbers of complete response letters in recent years. The number of CRLs that CDER issued took a dramatic drop in 2010 and stayed low through 2015. High

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'Between A Rock And A Hard Place,' Court Issues Injunction To Halt Praluent Sales

<http://bit.ly/2iQcOL2>

Regeneron and Sanofi have opportunity to appeal or to reach resolution with Amgen after district judge delays imposition of permanent injunction for 30 days in PCSK9 patent case.

US FDA Might Be Temporarily Headed By Ostroff As Califf Sets His Departure

<http://bit.ly/2jbMnf8>

Former acting commissioner in line for the temporary position again under FDA policy, unless incoming Trump administration designates someone else.

Rx Advertising: Can Consumers And Doctors Tell When Drug Promos Are Deceptive?

<http://bit.ly/2iLUZKC>

USFDA to assess whether consumers and healthcare professionals can detect and report false or misleading promotions; Bad Ad program could be expanded to consumers.

Merck KGaA Consumer Engages Social Media To Grow In Europe, Latin America

<http://bit.ly/2i0oJtT>

The German firm will expand its digital engagement strategy, having achieving strong followings with the strategy for three brands in Europe and/or Latin America. Initiative reflects company's larger "consumerization" strategy.

Agile's Phase III Data For Twirla Patch Fall Flat, Raise Doubts On Approval

<http://bit.ly/2ijOPjB>

Twirla low-dose birth control patch doesn't work as well in heavier women in Phase III SECURE study, but Agile believes that this is a class effect and an artifact of the stringent, real-world study design requested by FDA.



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goal. Most of those very fast approvals came with the help of FDA's popular new breakthrough therapy designation (BTD) program. Seven novel breakthrough products cleared CDER in 2016, with an average time to approval of 6.7 months.

However, the shortest time to approval of any CDER 2016 approval – three months for Biogen and Ionis Pharmaceuticals Inc's *Spinraza* (nusinersen) – went to a product that did not have a BTD. As the first therapy for the orphan disease spinal muscular atrophy, *Spinraza* nonetheless addresses a serious unmet medical need.

While BTD gives sponsors an advantage during review, thanks to intensive communication with the agency during development and an "all hands on deck" approach to reviews of BTD applications, the designation is not a guarantee of a first cycle approval. Three BTD products received CRLs in 2016 – Portola Pharmaceuticals Inc's *Andexxa* (andexanet alfa), BioMarin Pharmaceutical Inc's *Kyndrisa* (drisapersen), and Clovis Oncology Inc's *Xegafri* (rociletinib). Portola is working toward resubmission of the anticoagulant reversal agent with a narrower indication; Duchenne muscular dystrophy drug *Kyndrisa* and lung cancer therapy *Xegafri* were discontinued.

While FDA's review performance on priority review drugs was notable, the standard review class of 2016 set a contemporary record for the shortest average time to approval for standard review drugs. The seven standard review approvals in 2016 took an average of only 12.7 months. In contrast, the average standard review approval time for the previous five years works out to 17.5 months. ▶

Published online January 2, 2017

A Year Of Extremes

Fewer New Drugs, But With Higher Priority

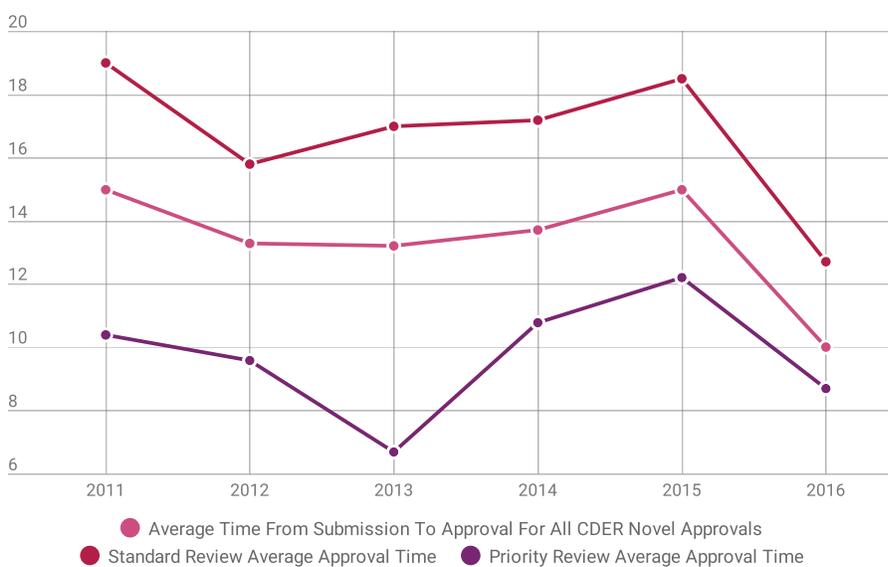


- 22** New molecular entities and novel therapeutic biologics approved by FDA in 2016
- 15** Priority review
- 7** Breakthrough therapy designations
- 9** Orphan drugs
- 8** First in class

Source: Pink Sheet's FDA Performance Tracker; FDA

Stellar Review Performance

Time to approval over time



- 21 of 22** Approvals met Prescription Drug User Fee Act goals
- 21 of 22** Approvals on the first review cycle

Source: Pink Sheet and FDA data



CLICK TO FIND THIS STORY ONLINE

To see an interactive chart of CDER's 2016 novel approvals, go to pink.pharmamedtechbi.com

US FDA Has Slim Advisory Committee Schedule – A Sign Of Things Not To Come?

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FDA's advisory committee calendar for drugs remains almost entirely bare, despite several applications with approaching user fee goals.

The agency has scheduled two advisory committee meetings in the new year. FDA's public calendar of advisory committee meetings has no listings as of its last update on Dec. 28.

It's listing of tentative meetings in 2017 also listed no expected meeting dates for CDER until a Jan. 3 update, when a Feb. 16 date was added for the Psychopharmacologic Drugs Advisory Committee, as well as a March 15 date for the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology.

The Feb. 16 date will be for Neurocrine Biosciences Inc.'s *Ingrezza* (valbenazine), proposed for treatment of tardive dyskinesia. The March 15 meeting is expected to address model-informed drug development approaches and strategies.

In January 2016, CDER conducted one and postponed another. The same month in 2015, it conducted three meetings. In February 2016, it conducted three meetings, after conducting two the same month in 2015.

ADDING 'VALUE TO THE PROCESS'

It is highly unlikely that the Center for Drug Evaluation and Research will go an entire year without conducting more than a couple of advisory committee meetings. However, a smaller schedule could indicate an increasing confidence by the Office of New Drugs (OND) that it will not always need outside advisors' opinions to make approval decisions.

Outgoing OND Director John Jenkins said the agency still thinks about whether an advisory committee is necessary as prescribed in the 2007 FDA Amendments Act, but now is finding they are not needed as often.

"I think over time we've become much more comfortable with focusing on where we think the advisory committee will add value to the process and where we think it's just adding more work to the process," Jenkins said Dec. 14 during the FDA-CMS Summit. "We consider whether an advisory committee is needed for every NME application that comes in and other types of applications, but often we find that there's not really the type of issues there that we think warrant that type of public presentation."

Sponsors certainly would appreciate being able to avoid the public spectacle that advisory committees can become and the preparation required to try and entice a positive opinion. But other stakeholders may worry should fewer NDAs go before a public meeting prior to an approval or complete response action.

Patients in particular have embraced the advisory committee process as a point where they can influence a drug's review, as evidenced by the controversial approval of Sarepta Therapeutics Inc.'s



Duchenne muscular dystrophy treatment *Exondys 51* (eteplirsen).

Yet, there also have been a number of cases where advisory committee meetings seem to result in confusion.

FDA has indicated it will conduct advisory committee meetings for most, if not all, of the biosimilar applications it receives for the time being. But it seems that committee members have been uncertain about the agency's biosimilar approval standards during some meetings, raising questions about how much value they add.

CHANGING INDUSTRY PRIORITIES?

Industry's changing priorities also may help explain the lack of scheduled advisory committee meetings. Jenkins also said that some recent NDAs have shown so much efficacy that a meeting has not been necessary.

"In some areas we're seeing much more effective drugs so the benefit-risk balance is very favorable, so some of those close calls that were the subject of advisory committees in the past where you're trying to balance a little bit of benefit against significant risk, are not as common as maybe they used to be," he said. "And I think also there's been a shift over time to development in oncology and rare disease areas where by design the benefit-risk calculus is different than a standard primary care drug."

A number of applications have user fee goals in January and February, but have no committee meeting scheduled. And given the tight timeframe, it is unlikely most of those will get a meeting unless there is a goal date extension by the review division or another delay.

Some also are undergoing priority review, which may diminish their ability to gain a committee meeting.

EMA Guidance On Investigational ATMPs To Focus On Exploratory And Pivotal Trials

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The European Medicines Agency's draft guideline on investigational advanced therapy medicinal products (ATMPs), which is expected to be released for stakeholder consultation in the first quarter of 2017, is to focus more on differentiating between what constitutes an exploratory trial and pivotal clinical trial, rather than between the different phases of a clinical trial.

During the drafting of the guideline, it became clear that the classical approach of distinguishing between the various stages of a clinical trial (e.g., Phase I, II, III) does not work well for ATMPs, said Ilona G Reischl, the Austrian representative on the EMA's Committee for Advanced Therapies.

There have been instances of companies first portraying a trial as "only a Phase II trial" but then when they apply for licensing later on, they describe the same trial as a pivotal trial, she added. As a result, it was decided that the guideline should focus on differentiating between exploratory clinical trials and pivotal clinical trials, she said.

Reischl was speaking at a conference organized jointly by the EMA and the European Biopharmaceutical Enterprises (EBE) on Dec. 16 in London, entitled "Optimising the development of ATMPs to meet patient needs".

"One way or the other, you [will] have to make clear what you want to use the data [from a clinical trial] for and the guidance will aim to make that clear," Reischl said.

She added that the draft guideline would focus on laying down minimal requirements for early clinical trials, but that guidance for later development would also be included "where it makes sense."

The guideline, she explained, will apply to all types of ATMPs and will cover quality, non-clinical and clinical aspects. Reischl said this in itself should be an indication to stakeholders that the guideline cannot not be "ultra-specific as we need to cover all types of ATMPs". There will be limitations in terms of providing only high- or medium-level guidance "as we can't include absolute details for specific types of products," she added.

The EMA's CAT is preparing the draft guideline on investigational ATMPs following a request from the European Commission.



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Though a large number of ATMPs are under development and are entering clinical trials, Reischl said that there is no dedicated guidance for investigational ATMPs.

She pointed out, for example, that the EU guideline on first-in-human clinical trials with investigational medicinal products specifically excludes gene and cell therapy products. "We have a definite gap," Reischl said.

Work on the guideline for investigational ATMPs began in 2016 and the EMA expects to release the final draft for stakeholder consultation in the first quarter of 2017. The guideline is being developed by CAT members, who have also sought input from national clinical trials assessors in various EU member states via the Clinical Trials Facilitation Group.

Reischl explained that while framing the guideline, the EMA decided to prepare separate text for cell-based products and gene therapy products. These separate texts will be brought together at a later stage, after any redundancies or similarities have been dealt with. ▶

From the editors of Scrip Regulatory Affairs. Published online January 3, 2017

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Data Integrity Lapses Continue To Erode Wockhardt

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Wockhardt Ltd. has begun the new year on a disappointing note after a US FDA warning letter referred to a range of current good manufacturing practice (CGMP) violations at the firm's Ankleshwar site in India, including those around data integrity.

The active pharmaceutical ingredient (API) unit in Ankleshwar has been under an FDA import alert since August 2016 and more recently in the news after Cempra Inc. indicated that resolution of deficiencies at Wockhardt's API site is among the prerequisites for getting its antibiotic Solithera (solithromycin) back on the approval path.

On Dec. 29, Cempra said FDA's complete response letter noted that additional clinical safety information and the satisfactory resolution of manufacturing facility inspection deficiencies are required before the NDA may be approved; Cempra, though, is already working on an alternate GMP manufacturing facility for solithromycin API.

UNRAVELED STITCHING, UNOFFICIAL NOTEBOOKS

The FDA warning letter against the Ankleshwar unit, dated Dec. 23 and now available on the agency's website, notes that for sterile APIs, the firm failed to establish and follow appropriate written procedures meant to prevent microbiological contamination of products purported to be sterile and that include validation of all aseptic and sterilization processes.

It also suggests that the clothing of the manufacturing personnel was not appropriate to protect products from contamination. The warning letter said that employees were working in gowns that had "unraveled stitching" extending from hoods, zippers and pants; it also maintained that the aseptic processing gowns were inadequate to prevent contamination of sterile products with "particles and microorganisms shed from



“Our investigator found discrepancies between these unofficial notebooks and the official data retained by your quality unit,” the warning letter said.

employees' bodies.”

Specific GMP deviations at the API unit include the failure to record activities at the time they were performed, and destruction of original records. FDA refers to several “unofficial” notebooks recording sample preparation for out-of-specification (OOS) investigations, route-of-synthesis experiments and scale-up data.

“Our investigator found discrepancies between these unofficial notebooks and the official data retained by your quality unit,” the warning letter said.

COMPREHENSIVE INVESTIGATION

The warning letter also suggests that the Wockhardt's data integrity remediation efforts are insufficient.

It maintains that the quality system “does not adequately ensure” the accuracy and integrity of data to support the safety, effectiveness and quality of the drugs manufactured and recommends that a qualified consultant be retained to assist in the remediation effort.

The agency requested a comprehensive investigation into, among others, the extent of the inaccuracies in data records and reporting, including an assessment of the extent of data integrity deficiencies at the site.

“Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses,” the warning letter said.

Wockhardt's Waluj and Chikalthana units in India are also under import alert, and in July 2016 the company said that it had received an establishment inspection report (EIR) for the units with certain observations. Data integrity concerns had been cited at the Waluj and Chikalthana unit as well previously.

An EY (formerly Ernst & Young) survey around data integrity compliance issues in the Indian pharmaceutical sector had earlier thrown up some potentially worrisome findings, including an absence of quality processes and procedures at some firms amid work pressure and manpower shortages, though there has been sustained effort among several frontline domestic firms to improve compliance.

EFFORTS TO RESOLVE ISSUE

Reacting to reports on the warning letter for the Ankleshwar unit, Wockhardt said that the import alert had already been effected in August 2016 and that the warning letter

is part of the “same process” of the FDA.

The company informed the Bombay Stock Exchange that it has already initiated “required steps” to address the concerns raised by the FDA and is “putting all its efforts to resolve the same.”

Some analysts referred to Wockhardt’s past assurances toward creating a “global quality system” and shoring up quality-related staff, in the backdrop of the “generally unchanged” compliance record of the firm. In November, FDA issued a

warning letter to CP Pharmaceuticals Ltd., a stepdown subsidiary of the company in the UK, but the company said that no business was being conducted from the arm to the US market.

Some analysts were also surprised at the sequence of the FDA’s actions – the import alert followed by a warning letter – though the agency has in the past, in another instance, indicated that it takes a complementary import alert action along with the issuance of warning letters when

it has serious concerns about the quality of products shipped by a drugs firm.

“These activities are not always concurrent. FDA is committed to taking timely actions to maintain a high quality drug supply, and the warning letter emphasizing the international facility’s violations may precede or follow the import alert action,” FDA told Scrip at the time. ▶

From the editors of PharmAsia News.

Published online January 4, 2017

CONSUMER PRODUCTS

Primatene Mist CRL Underscores Challenges For OTC Asthma Treatments

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Amphastar Pharmaceuticals Inc. keeps its eye on the goal of making its asthma inhaler *Primatene Mist* available OTC again as a second complete response letter from FDA pushes the finish line back further.

Amphastar on Dec. 27 announced it received a CRL on the firm’s new drug application for making *Primatene Mist* available reformulated with the original active ingredient, epinephrine, but with hydrofluoroalkane replacing ozone-depleting chlorofluorocarbons as a propellant.

In its release, Amphastar said the CRL requests that it make additional changes to the labeling and packaging for *Primatene Mist* and also another human factor validation study to assess consumers’ ability to use the actuated, or breath-triggered, epinephrine inhalation aerosol without the guidance of a doctor or pharmacist.

The second CRL, roughly two years after the first in late 2014, likely adds as much as 18 months to the time needed before Amphastar could re-launch the OTC product after receiving approval of its NDA by satisfying FDA’s concerns about consumers correctly using the product without a doctor’s intervention.

The Rancho Cucamonga, Calif., firm, which would market *Primate Mist* through its Armstrong Pharmaceuticals Inc. subsidiary, said it is evaluating the request and plans further discussions with FDA.

CEO Jack Zhang said Amphastar intends “to continue to work with the FDA during the post-action phase to address their concerns in the CRL by the middle of 2017 and bring *Primatene Mist* back to the OTC market as soon as possible.”

In a same-day research note, Jefferies analysts said Amphastar’s NDA still appears “approvable” as FDA has not questioned *Primatene Mist*’s safety. They said they expect the CRL will delay the product’s return to market by between one year and 18 months.

“We expect the necessary studies will be reasonably short and

“We expect the necessary studies will be reasonably short and inexpensive, but note that the letter does represent a meaningful delay in the approval timeline.”

– Jefferies analysts’ research note

inexpensive, but note that the letter does represent a meaningful delay in the approval timeline,” according to the Jefferies note.

Although Amphastar previously identified the reformulated product as *Primatene HFA* – deleting *Mist* from the name and adding an abbreviation for hydrofluoroalkane – the firm now refers to the product by its original brand.

The proposed product includes a built-in spray indicator and replaces the glass container used in the original *Primatene Mist* product with a pressurized metal canister. A representative of the firm did not respond to requests to comment on the CRL and on plans for the NDA.

QUESTIONS ON SAFE USE, NOT INGREDIENT SAFETY

Although FDA does not question epinephrine’s safety, the additional questions stated in the CRL about labeling and about actual use indicate agency officials are not convinced that OTC access to an emergency asthma inhaler is safe for consumers.

“The prior CRL also required further study of label comprehension, behavioral and actual use and an assessment of consumers’ ability to use the device over-the-counter. The fact that [Amphastar] seemingly completed FDA’s prior requests makes today’s news

CONSUMER PRODUCTS

somewhat surprising," Jefferies analysts noted.

A joint panel of the Nonprescription Drugs and Pulmonary-Allergy Drugs advisory committees in early 2014 voted 18-6 to recommend against approving the reformulated product. The panel, which also voted 17-7 that Amphastar did not prove the product's safety, noted that the firm had not conducted an actual use trial to show consumers would appropriately follow use and cleaning instructions to avoid the risk of clogs and under- or over-dosing.

Primatene Mist was withdrawn from the market in 2011 due to environmental concerns about the use of the chlorofluorocarbon as a propellant, not because of safety or efficacy concerns, but experts have told FDA they doubt the benefit of making asthma treatments available nonprescription. Some health care providers and researchers contend asthma patients could be unaware their condition is worsening because they forgo necessary treatment when they rely on OTC inhalers.

Questions about an OTC indication for an asthma treatment also prompted Merck & Co. Inc. in 2014 to request approval for a nonprescription version of its Rx asthma treatment blockbuster *Singulair* with an indication only for allergy relief in adults. Nevertheless, NDAC members discouraged FDA from OTC approval of montelukast 10mg partly due to off-label use risk. Merck &

Co. has not commented on its plans for an OTC Singulair since then. Meanwhile, two asthma treatments marketed OTC that have attracted FDA warnings remain available, but likely would be targets of more consequential enforcement action should the agency approve Primatene Mist or another OTC asthma treatment proposed in an NDA.

The agency in March 2016 warned Dr. Natural Healing Inc. that its oral epinephrine inhaler should not be available because its dry powder delivery is not approved under the OTC bronchodilator monograph; and FDA previously warned that Nephron Pharmaceutical Corp.'s *Asthmanefrin* racepinephrine product sold with the battery-powered EZ Breath Atomizer also was non-compliant with the monograph.

Dr. Natural Healing's *Prime Asthma Relief* still is featured on its website, which include sales capability, but the Milford, Del., firm's Dr. Natural added a notice on Nov. 4 stating that the product is out of stock for up to three weeks.

Asthmanefrin remains available at retailers. Orlando, Fla.-based Nephron Pharmaceutical does not offer sales of its products, which also include Rx generic inhalers, on its website. ▶

From the editors of Tan Sheet. Published online January 4, 2017

GENERIC DRUGS

FDA's ANDA Approvals

SPONSOR	ACTIVE INGREDIENT	DOSAGE; FORMULATION	APPROVAL DATE
Unique Pharmaceutical	Glipizide	2.5 mg, 5 mg and 10 mg; extended-release tablet	12/29/2016
Micro Labs	Amoxicillin/ clavulanate potassium	875 mg/EQ 125 mg base; tablet	12/29/2016
Breckenridge	Bendamustine HCl	25 mg/vial and 100 mg/vial; power for IV infusion	12/29/2016
RiconPharma	Nystatin/ triamcinolone acetonide	100,000 units/gm/ 0.1%; topical ointment	12/29/2016
Apex	Cyproheptadine HCl	4 mg; tablet	12/29/2016
Micro Labs	Amoxicillin/ clavulanate potassium	250 mg/EQ 125 mg base; 500 mg/EQ 125 mg base; tablet	12/30/2016
Teligent	Clindamycin phosphate	EQ 1% base; topical solution	12/30/2016
Aurobindo	Levalbuterol HCl	EQ 0.0103% base, EQ 0.021% base and EQ 0.042% base; inhalation solution	12/30/2016
Teligent	Flurandrenolide	0.05%; topical ointment	12/30/2016
Teligent	Nystatin/ triamcinolone acetonide	100,000 units/gm/ 0.1%; topical ointment	12/30/2016
Appco	Glycopyrrolate	1 mg and 2 mg; tablet	01/03/2017
Sun	Ipratropium nromide	0.02%; inhalation solution	01/03/2017
Tentative Approvals			
PharmCare	Tenofovir disoproxil fumarate	300 mg; tablet	12/29/2016
Lupin	Pitavastatin calcium	EQ 1 mg base, EQ 2 mg base and EQ 4 mg base; tablet	12/29/2016
MSN Labs	Fingolimod	0.5 mg; capsule	12/29/2016

Brand vs. Brand Patent Battles Heat Up, Focus On Big Drug Classes

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The Merck & Co. Inc. vs. Gilead Sciences Inc. litigation over hepatitis C treatment patents put a spotlight on the stakes involved when brand-name pharmaceutical companies go up against each other.

In December, a Delaware jury found that Gilead willfully infringed a Merck patent and awarded Merck damages of \$2.45bn, a record-breaking verdict in an infringement case. And in a separate case earlier in the year, a California jury found Gilead's *Sovaldi* (sofosbuvir) and *Harvoni* (ledipasvir/sofosbuvir) infringed two other patents and awarded Merck \$200m. However, Merck lost the award when a judge subsequently found it had engaged in misconduct. Gilead is now seeking \$15.5m in attorneys' fees in the case.

While brand-name drug makers routinely fight generic companies over their patents, brand vs. brand disputes are far less frequent. According to the legal analytics firm Lex Machina, innovator drug makers filed 467 infringement suits in response to generic manufacturers' abbreviated new drug application filings in 2015.

There are no similar statistics on the litigation between big pharma companies but a review of company SEC filings indicates that they are relatively infrequent compared to ANDA cases. They typically involve competitors in a lucrative drug class, from the recent litigation between makers of anti-PD-1 immunotherapies to the previous dispute between Pfizer Inc. and Eli Lilly & Co. over erectile dysfunction patents (*see chart of select cases, p. 12*).

Paul Ragusa, a partner at Baker Botts, said he has seen an increase in litigation between brand-name companies. He pointed to two factors for the uptick: consolidation in the industry and the patent cliff, the steep decline in revenues that occurs when patents on key products expire.

"Companies are looking at their IP portfolio and deciding how to best protect not only the portfolio protecting their product but the portfolio that may cover alterna-

tive methods of administration," Ragusa said.

DIFFERENT KIND OF FIGHT

The litigation between brand-name firms is different from ANDA battles. One contrast is in timing. A brand company does not have to wait for a Paragraph IV notice to sue another brand company who commercializes an alternative (non-ANDA) product as it must do in disputes with generic manufacturers. Ragusa noted that there are also differences in how generic and brand companies budget litigation and pick their defenses.

For example, he said Teva Pharmaceutical Industries Ltd. files a lot of Paragraph IV notices certifying that its ANDAs do not infringe the innovator's patents or that the patents are invalid and has a budget for handling the ensuing litigation. To meet that budget, the company may drop some infringement defenses along the way. But he said that may not be the case when two brand-name powerhouses go after each other.

The most common infringement defenses are that a company is not infringing, and that the brand's patent is invalid based on prior art or because the patent's specifications failed to meet requirements of Section 112 of the Patent Act, which include having a complete written description of the claimed invention and sufficient specificity.

Another distinction in brand litigation is the potential for settlements. While generic firms are open to settlement as it gives them a chance to launch the first generic, Ragusa said brand-name competitors are looking to market their own full-scale products so will go the distance.

The outcome though is uncertain. PricewaterhouseCoopers' 2016 patent litigation study reported that the patent holder's overall success rate (trial and summary judgment combined) for all industries from



1996-2015 was approximately 33%. Those in the biotech/pharma sector had a higher success rate of about 40%. The study did not specify if the litigation was between brand-name companies or included both brand-name and generic cases.

The report notes that the largest damages award – which was surpassed by the verdict for Merck – was the \$1.67bn Johnson & Johnson's Centocor Ortho Biotech unit received in its suit against Abbott Laboratories Inc. alleging infringement of its *Humira* (adalimumab) patent. The Federal Circuit overturned the verdict in 2011.

SANOFI/REGENERON DENIED NEW TRIAL IN PCSK9 PATENT FIGHT

The headline cases naturally involve blockbuster products. In the Merck-Gilead dispute, Gilead's two hepatitis C drugs had US sales of \$25.4bn through August 2016. FDA approved *Sovaldi* in December 2013 and *Harvoni* in October 2014. Merck's hepatitis C drug *Zepatier* (elbasvir/grazoprevir), approved in January 2016, had sales of \$326m for the nine months ended Sept. 30.

In another major case, Amgen Inc. won a jury verdict in March that patents covering its PCSK9 inhibitor *Repatha* (evolocumab) are valid. Amgen filed suit against Sanofi and Regeneron Pharmaceuticals Inc. in October 2014 alleging that their anti-PCSK9 antibody *Praluent* (alirocumab) infringed Amgen patents. *Repatha* was approved in August 2015 and *Praluent* was approved in July 2015.

Prior to the trial Sanofi and Regeneron stipulated that they infringed the patents at issue. On Jan. 3, Delaware District Court Judge Sue Robinson issued orders denying Sanofi and Regeneron's motions for judgment as a matter of law that the patent specification lacked written description of the invention and was not enabled and for a new trial.

In a memorandum opinion, Judge Robinson said “viewing the record in the light most favorable to plaintiffs, substantial evidence supports the jury’s verdict.”

Amgen has filed a motion for a permanent injunction which the judge has yet to rule on. Sanofi and Regeneron are appealing the jury verdict. Barclays analysts said in a Jan. 3 note that the judge could rule to remove Praluent from the market or allow the drug to remain and assign a royalty, either decision of which would likely be appealed. They said they expect Sanofi and Regeneron will ultimately pay Amgen some sort of royalty on sales.

In other ongoing litigation, Bristol-Myers Squibb Co. and Ono Pharmaceutical Co. Ltd. claim Merck’s anti-PD-1 immunotherapy *Keytruda* (pembrolizumab) infringes patents relating to *Opdivo* (nivolumab).

Brand-name battles are also likely to increase as more biosimilars come on the market. Biotech giants AbbVie Inc. and Amgen are in litigation over Amgen’s *Amjevita* (adalimumab-atto), a biosimilar to AbbVie’s Humira. AbbVie sued Amgen for infringement in August and FDA approved Amjevita in September. It is the first approved Humira biosimilar and the fourth biosimilar to clear the agency.

In another biosimilar case, Janssen Biotech Inc.’s suit against Celltrion Inc. and Pfizer unit Hospira Inc. remains ongoing after Pfizer launched *Inflextra* (infleximab-dyyb), a biosimilar to Janssen’s *Remicade* (infleximab), in the US in November. A jury trial is scheduled to begin on Feb. 13, 2017 to determine if Inflextra infringes Janssen’s cell culture media patent.

Given the battles of 2016, it seems likely that brand-name companies will be going into the ring against each other more frequently in the coming year. ▶

Published online January 4, 2017

Brand vs. Brand Litigation

Below are some of the patent battles waged between brand-name pharma companies over the past six years.

CASE	DISPUTE	STATUS
<p>Idenix Pharmaceuticals LLC (Merck & Co. Inc.) v. Gilead Sciences Inc. 14-cv-00846, District of Delaware</p> <p>Gilead Sciences Inc. v. Merck & Co. Inc. 13-cv-04057, Northern District of California</p>	<p>Idenix filed suit against Gilead in December 2013 alleging Gilead’s hepatitis C drugs Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir) infringe two patents. Claims asserted against one patent were later dropped. Merck acquired Idenix in 2014.</p> <p>Gilead filed suit in August 2013 seeking a declaratory judgment that it does not infringe two other patents covering compounds and methods used to develop hepatitis C treatments.</p>	<p>In December, a Delaware jury found Gilead willfully infringed the patent and awarded Merck \$2.45bn in damages. Judge is to decide if Gilead must pay a penalty for willful infringement and additional royalties on future sales of Sovaldi and Harvoni. Gilead is appealing to the Federal Circuit</p> <p>California jury found that Merck’s patents are valid and awarded the company damages of \$200m. A judge subsequently found that Merck engaged in misconduct, vanquishing the award. Gilead is seeking \$15.5m in attorneys’ fees.</p>
<p>AbbVie Inc. v. Amgen Inc. 16-cv-666, District of Delaware</p>	<p>AbbVie claims Amgen’s Humira (adalimumab) biosimilar infringes 10 patents.</p>	<p>Complaint filed in August in Delaware District Court. Amgen filed counterclaims of non-infringement and invalidity.</p>
<p>Janssen Biotech Inc. v. Celltrion Inc./Hospira (Pfizer Inc.) 15-cv-10698, District of Massachusetts</p>	<p>Janssen filed suit claiming Celltrion/Pfizer’s Inflextra, a biosimilar to Remicade (infleximab), infringes several patents.</p>	<p>Massachusetts district court judge ruled in August that a Janssen patent covering the infliximab antibody is invalid for obviousness-type double patenting. A jury trial is to begin in February 2017 to determine if Inflextra infringes a cell culture media patent.</p>
<p>Bristol-Myers Squibb Co./ Ono Pharmaceutical Co. Ltd. v. Merck 14-cv-01131, District of Delaware</p>	<p>Bristol and Ono filed suit in September 2014 claiming Merck’s marketing of Keytruda (pembrolizumab) will infringe patent No. 8,728,474 covering use of antibodies that bind to PD-1 to treat cancer. BMS used the invention to develop Opdivo (nivolumab).</p>	<p>The suit was filed the same day FDA approved Keytruda.</p> <p>In June 2015, Ono filed suits alleging infringement of two other patents (Nos. 9,067,999 and 9,073,994). In June 2016, Merck filed petitions for inter partes review challenging the validity of these patents.</p> <p>In April 2016, Merck filed declaratory judgement action against BMS and Ono seeking a ruling that two other patents (Nos. 8,779,105 and 9,084,776) are invalid and/or not infringed by the sale of Keytruda. BMS and Ono filed a counterclaim of infringement in June.</p>
<p>Amgen Inc. v. Sanofi/ Regeneron Pharmaceuticals Inc. 14-cv-01317, District of Delaware</p>	<p>Amgen claims Sanofi’s Praluent (alirocumab) infringes patents covering its PCSK9 inhibitor Repatha (evolocumab). Both drugs were approved in 2015.</p>	<p>In March 2016 Delaware jury found Amgen’s Repatha patents are valid. On Jan. 3, district court judge denied Sanofi/Regeneron’s motions for a new trial and a judgement as a matter of law. Judge has yet to rule on Amgen’s motion for a permanent injunction.</p>

INTELLECTUAL PROPERTY

CASE	DISPUTE	STATUS
Merck Sharp & Dohme Corp. v. Genentech Inc. and City of Hope 16-cv-4992, Central District of California	Merck filed complaint in July 2016 seeking declaratory judgement that patent No. 7,923,221 (the Cabilly III patent) is invalid and that Keytruda and Zinplava (bezlotoxumab) do not infringe it.	Roche's Genentech unit and City of Hope filed a counter-claim for infringement. Merck filed two inter partes review petitions challenging the validity of claims in patent No. 6,331,415 (the Cabilly II patent). Patent Trial and Appeal Board denied institution of one petition and instituted review of the other petition and joined it with Mylan Pharmaceuticals Inc.'s IPR petition.
AbbVie v. MedImmune LLC 16-cv-01129, District of Maryland	AbbVie sought a declaratory judgement that a MedImmune patent covering Humira is invalid and it should thus no longer have to continue paying royalties on it.	The suit was filed in April 2016. The parties stipulated to dismissal of the suit in June.
Sanofi-Aventis US LLC v. Astra-Zeneca Pharmaceuticals LP and Amylin Pharmaceuticals LLC 15-cv-00662, District of Delaware	Sanofi filed complaint in July 2015 seeking declaratory judgement that its proposed GLP-1 agonist lixisenatide does not infringe three AstraZeneca patents and that the patents are invalid.	In July 2016 FDA approved Sanofi's Adlyxin (lixisenatide) once-daily injection for type 2 diabetes and in October the parties agreed to dismiss all claims and counterclaims.
Novartis Vaccines & Diagnostics Inc. v. Pfizer Inc. GlaxoSmithKline Biologicals SA v. Pfizer 15-cv-01283, District of New Jersey	Novartis' February 2015 complaint alleges Pfizer's sale of its Trumenba (meningococcal group B vaccine) infringes six patents.	GlaxoSmithKline took over the litigation with its acquisition of Novartis' vaccine business and filed an amended complaint in April 2015 asserting the same patents. It filed a second amended complaint in March 2016 asserting infringement of 12 patents.
Morphys AG v. Janssen Biotech Inc./Genmab US Inc. 16-cv-00221, District of Delaware	Morphys filed complaint in April 2016 alleging Janssen's anti-CD38 antibody Darzalex (daratumumab) infringes patent No. 8,263,746.	Janssen, which licenses rights to Darzalex from Genmab, filed a motion to dismiss the suit in June. FDA granted Darzalex accelerated approval for treatment of multiple myeloma in November 2015. Morphys is developing a competing antibody to CD38, MOR202.
Juno Therapeutics Inc. v. Novartis Pharmaceuticals Corp. 13-cv-01502, Eastern District of Pennsylvania	Patent and contract dispute over chimeric antigen receptor T-cell (CAR-T) technology was originally between St. Jude Children's Research Hospital and University of Pennsylvania. Juno took over for its partner St. Jude and Novartis intervened on behalf of UPenn.	In April 2015, Novartis agreed to pay Juno an initial \$12.5m plus future milestone payments and royalties.
Centocor Ortho Biotech Inc. v. Abbott Laboratories Inc. 2010-1144, US Court of Appeals for the Federal Circuit	J&J unit alleged Abbott's Humira infringed its patent claiming antibodies and antibody fragments that bind tumor necrosis factor-alfa.	In 2011, Federal Circuit overturned a \$1.67bn jury verdict against Abbott, finding J&J's patent claims were invalid because they did not include an adequate written description of what the patent covers.
Ariad Pharmaceuticals Inc. v. Eli Lilly & Co. 2008-1248, Federal Circuit	Ariad alleged Lilly's osteoporosis drug Evista (raloxifene) and sepsis treatment Xigris (drotrecogin alfa) infringed its patent.	In 2010, en banc Federal Circuit panel reaffirmed three-judge panel ruling that Ariad's patent claims were invalid because they did not provide an adequate written description of what the patent covers.
Pfizer v. Eli Lilly 02-cv-01561, District of Delaware	Pfizer alleged Lilly's erectile dysfunction drug Cialis (tadalafil) infringed its method-of-use patent for Viagra (sildenafil).	Pfizer dropped the complaint in March 2010, ending an eight-year battle. The agreement came after the US Patent and Trademark Office's Board of Patent Appeals and Interferences rejected the patent claim.
Amgen v. Roche 05-12237, District of Massachusetts	Amgen claimed Roche's Mircera (epoetin beta) infringed patents on its erythropoietin drugs Epogen (epoetin alpha) and Aranesp (darbepoetin alfa).	In 2007, jury found Mircera infringed several Amgen patents and in October 2008 district court judge issued permanent injunction. Roche subsequently obtained a license from Amgen allowing it to launch Mircera in mid-2014.



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Colombia's Glivec Pricing Means "Worst Of Scenarios" For Pharma Industry

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Colombia's research-based pharmaceutical industry association, AFIDRO, is preparing to take the government to court over new pricing regulations that follow the controversial declaration of public interest (DPI) for Novartis AG's *Glivec* (imatinib) and the subsequent price cut.

According to association CEO Gustavo Morales, "IP rights in Colombia have been gravely damaged" and some companies may be deterred from bringing their drugs to Colombia as a result of the government actions.

AFIDRO is concerned that recent events in Colombia – including the DPI for *Glivec*, the subsequent price cut and the new regulations on medicine prices – will undermine intellectual property rights and set a worrying precedent that will make international companies think twice about launching in Colombia. "There are other countries with similar a market size and with similar incentives that don't have this kind of threat to their intellectual property protections. So if I were in the board of one company, I would look at Peru, Chile or Mexico," Morales said.

Novartis also is challenging the health ministry's decision to declare *Glivec* to be of public interest. The move came after civil society groups requested that the health ministry issue a compulsory license for *Glivec*, arguing that the patent was weak, that the drug was expensive and that generic competition could bring the price down.

What followed the DPI was not a compulsory license, but a price cut. The health ministry announced it was reducing the price by 44%, from 368 pesos (US\$0.12) per mg to 206 pesos (US\$0.7) per mg, and the decision was made final Dec. 21. The formula for the price cut was in line with new regulations, published in November, for setting the price of a medicine that is declared to be of public interest. Under the new regulations the list of 17 countries

which Colombia references will be revised according to whether there is competition in the market between a brand and a generic. The lowest average price will be used as a basis for the Colombian price.

AFIDRO supports Novartis' legal action and is launching its own. It says in the new year it will challenge the government on the new pricing regulation in the courts. According to Morales, a declaration of public interest should not be used for anything

other than a compulsory license. "Using a DPI as an excuse to make a price cut is completely illegal and leaves us in the worst of any scenarios because it leaves us in the scenario in which a declaration of public interest can be used for whatever purpose the government wants." He maintains that according to the law a DPI can only be used to bring about a compulsory license. Morales worries that abuse of the law may eventually go further: "today it will be a price cut, tomorrow it could be for a regulatory issue, like marketing authorization."

AFIDRO is challenging the government on the grounds that the regulations are discriminatory and unconstitutional. According to Morales, the constitution stipulates that the government must promote and protect intellectual property rights. The new regulations target specific patented medicines with "more severe rules" than those set out by the general price regulations, he says. Only a patented medicine can be a subject of a DPI because the DPI is itself a prerequisite for a compulsory license – there is no need to issue a compulsory license if there is no patent protection. The regulation, therefore is discriminatory, argues Morales.

WHAT COMES NEXT?

AFIDRO is concerned about what might happen next, particularly because it maintains that the health ministry has no real grounds for declaring *Glivec* to be of public interest.

There is no public health crisis and no one who needs the drug is going without, says Morales. He adds that the price of *Glivec* has been under price controls for some time and that the drug is on the compulsory formulary, which means private insurers and public programs have to offer the drug to patients. The "flimsy" nature of the DPI has ramifications for other products, he believes. "If *Glivec* is a public interest medicine every other medicine,

A CONTENTIOUS HISTORY

Glivec, which is listed on the World Health Organization's essential medicines list, has been a contentious medicine in Colombia since its launch. The Colombian patent office declined to issue a patent for *Glivec* when Novartis first brought it to the country. Nevertheless, Novartis kept it on the market where it faced competition from generic versions, and challenged the decision. In 2013 the company won, a patent was issued and generic rivals were withdrawn.



“Novartis had already made \$47bn in global sales on Glivec there is surely no rationale for earning back R&D costs”

especially those that are complex, high-cost and innovative, could be subject to the same treatment. If a product is subject to a DPI, it will also be subject to a specific price regulation,” says Morales. He points to procedures to issue DPIs for hepatitis C treatments that are underway. The same NGOs that requested a compulsory license for Glivec are now pushing for a DPI to make hepatitis C treatments more accessible, including Gilead Sciences Inc.’s *Sovaldi* (sofosbuvir), Bristol-Myers Squibb Co.’s *Daklinza* (daclatasvir) and Merck & Co.’s *Victralis* (boceprevir).

PROTECTING PUBLIC HEALTH

The groups that are fighting for the DPIs – IFARMA, Misión Salud and CIMUN – say that the Glivec DPI is necessary to protect the public health budget. They welcome the price reduction but say bigger savings

for the public health system are possible and want the patent office to proceed with a compulsory license. This could lead to a price of just 68 pesos per mg and was the price of one of the generics available on the market before Glivec’s patent was granted.

The groups say that they are committed to defending the right for people to health and access to care, which are “reflected in protecting the public health budget and enforcing the implementation of public health safeguards contained in the trade agreements signed by Colombia, such as TRIPS, the Doha Declaration and the Colombian-Switzerland investment agreement.” They urge governments to make full use of the their “right to comply with their obligations of protecting, respecting and fulfilling the human right to health.”

They add that the DPI for hepatitis C drugs is necessary because the latest gen-

eration of treatments are on sale in many markets at unaffordable prices for out of pocket payers and public payers.

The NGO Health Action International says it “supports the move to issue a declaration of public interest for imatinib (marketed as Glivec), which is on the WHO’s essential medicines list and which Novartis was selling for a price in Colombia per patient that is approximately twice the Colombian gross national income per capita.

“There was no willingness from Novartis to voluntarily lower the price in Colombia and given that Novartis had already made \$47bn in global sales on Glivec there is surely no rationale for earning back R&D costs. Colombia is a small market for Novartis which means it has less clout in price negotiations and they are fully dependent on companies to lower the price of drugs voluntarily. If this does not happen they are fully entitled to use the legal means available and compliant with international law to lower the price of a drug,” says HAI. ▶

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LEGISLATION

Senate Committee Closes Books On 2016 Pricing Investigation; PBMs In Hot Seat Next?

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The Senate Aging Committee’s final report on price spikes for off-patent drugs ends up roughly where the investigation began: with a call for steps to encourage competition for older products, but nothing close to a serious threat to the generally free pricing environment in the US.

The report closes the books on the committee’s investigation into a series of price increases by four companies that helped frame the debate over drug pricing in 2016: Turing, Valeant, Retrophin and Rodelis. While that investigation highlighted some notorious figures in industry and helped paint the pharmaceutical sector in a very bad light, the actual themes of the Aging Committee investigation were relatively safe for innovator companies.

The focus throughout was largely on barriers to competition in the regulatory process for generics, and on drawing a line between companies that rely on “repricing” rather than R&D to drive growth – not on the high launch prices for new drugs or even on the an-

nual price increases for blockbuster brands.

The Aging Committee has no legislative jurisdiction, so the report does not lead to any next steps unless and until another committee decides to take up the issue in 2017. That makes the impact of any recommendations uncertain to say the least. The

One of the few topics of the investigation that threatened to open up into a broader challenge for innovator companies during the hearing process was the discussion of the role of patient assistance and couponing in enabling high prices.

pre-Christmas timing of the report's public release (Dec. 21) further undercuts any sense that the next step from the investigation will be changes to pricing policy in the US.

Still, even if each of the half dozen recommendations in the report were followed to the letter, the impact on most Big Pharma companies would be minimal. (See box)

PATIENT ASSISTANCE PLANS WARRANT 'FURTHER STUDY'

One of the few topics of the investigation that threatened to open up into a broader challenge for innovator companies during the hearing process was the discussion of the role of patient assistance and couponing in enabling high prices.

While the committee report does include the couponing issue as a policy focus, the discussion lacks any specific next step. "The Committee found that self-serving motives were often critical to understanding patient assistance programs and is concerned that patient assistance can be used to steer patients toward higher priced drugs, resulting in higher expenditures for beneficiaries, federal health care programs, and commercial providers," the summary states.

However, rather than call for a specific response, the summary concludes: "The Committee finds this issue warrants further study." Later on in the report, the committee presents a fairly balanced discussion of the conundrum: patient assistance undeniably helps individuals who might otherwise not be able to afford necessary medications.

Preserving that virtue while attempting to assure that the programs are not "so narrowly focused that they operate simply as a means by which pharmaceutical companies can subsidize the purchase of their own products" is easier said than done.

GENERICS, IMPORTATION, PBMS

In contrast, the other recommendations are much more immediately actionable, including the unsurprising endorsement of specific bills related to prioritizing generic drug reviews and addressing limited distribution programs as a barrier to generics. The generic drug priority review issue is certain to be addressed in the GDUFA reautho-

rization process next year, and there is bound to be another strong push for legislation to curb perceived abuses of the REMS process.

However, even much longer shot proposals like allowing targeted importation of unapproved drugs in the face of price spikes are much more fully fleshed out in the Aging Committee report than the discussion of copay coupons. The specific idea proposed by the Aging Committee is very different than the broad reimportation proposals that have been debated for that past 15 years, but it is laid out in the report in a fashion that at least allows it to be put on the table in the near term. There is no similar statement of an actionable next step on co-pay coupons.

The report includes a coda noting that there are other issues about drug pricing that have emerged in the context of products like *EpiPen* and *Narcan* that weren't part of the investigation. Still, the committee offers two possible areas worthy of further exploration – including digging into PBM practices.

"Another area worthy of further study is the role of PBMs," the report states. "While some experts claim that PBMs function to keep down the price of drugs, other have suggested that PBMs may be contributing to part of the drug pricing problem. The Committee does not have visibility into this area from its investigation due to the fact that PBMs played a limited role in the drugs investigated by the Committee." ▶

From the editors of the RPM Report. Published online January 3, 2017

PROPOSED POLICY RESPONSES TO PRICE SPIKES

1. Enact the Increasing Competition in Pharmaceuticals Act of 2016 to provide solutions to regulatory uncertainty, small market size, and other factors that serve as limitations to generic entry by incentivizing competition.
2. Encourage generic competition by ensuring the right to obtain samples and simplifying Risk Evaluation and Mitigation Strategies.
3. Allow highly targeted temporary drug importation to combat major price increases in off-patent drugs to provide prompt price relief.
4. Prevent the misuse of patient assistance programs and copay coupons.
5. Reinvigorate the Federal Trade Commission to enforce action when it comes to drug company mergers, operations, and drug market dynamics.
6. Improve transparency in the health care system.

Source: "Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System," Report by the Senate Special Committee on Aging, released Dec. 21.

Biosimilars Ineligible For Reduced Medicaid Rebates As Authorized Generics

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The Centers for Medicare and Medicaid Services closed off the possibility that biosimilars could be eligible for reduced Medicaid rebates as authorized generics in a recent notice to manufacturers.

"A biosimilar biologics product approved under a BLA should not be treated as an authorized generic for the purpose of the [Medicare drug rebate] program," CMS states in the Dec. 21 notice..

By law, most single-source outpatient drugs are subject to a minimum rebate equaling 23.1% of the drug's average manufacturer's price (AMP), and generic drugs are subject to a minimum rebate equaling 13% of the AMP. CMS' position means that biosimilars are subject to the higher brand rebate.

The notice adds that pricing for a biosimilar treated as an authorized generic should not be included in AMP calculations for its reference drug.

The biosimilar "should not be ... included in the sales of the manufacturer of the reference biological product to the manufacturer of the biosimilar biological product when calculating AMP because it is neither marketed under an NDA nor able to be classified as an 'I' drug," CMS says. Authorized generics are designated as innovator multiple source or "I" drugs in Medicaid drug rebate system.

Furthermore, CMS maintains, "because biosimilar biologics are single source drugs, the best price of the reference biologic and the biosimilar biologic should be determined as the lowest price available from each manufacturer."

The announcement elaborates on CMS' earlier-stated general position that biosimilars should be treated as single-source drugs in the Medicaid drug rebate program.

CMS POLICIES IN MEDICARE ALSO CREATE OBSTACLES

The position has caused consternation among biosimilar developers hoping for more of a reimbursement incentive in



The announcement elaborates on CMS' earlier-stated general position that biosimilars should be treated as single-source drugs in the Medicaid drug rebate program.

Medicaid. It has also contributed to the view that CMS reimbursement policies do not promote use of biosimilars.

The Affordable Care Act provides an important incentive for biosimilars in Medicare Part B by requiring that physicians be paid the average sales price of a biosimilar plus 6% of the innovator drug price (which would be higher than 6% of the biosimilar price).

But in implementing the law, CMS has adopted a Part B reimbursement coding policy for biosimilars that is consistent with the way it pays for generics, which is viewed as an impediment for biosimilars.

Part B will pay for all biosimilars referencing the same drug using one reimbursement code, as it does for generics, under the CMS policy. This means physicians will be paid for biosimilars based on the weighted average sales price for all products within each shared Healthcare Common Procedure Coding System (HCPCS) code.

The plan has generated opposition from providers, manufacturers and members of Congress.

Biosimilars also face a disadvantage in Medicare Part D. CMS has concluded that biosimilars should not be subject to the 50% discount required for branded drugs provided to seniors who have reached the Part D coverage gap. However, that sets up a situation where biosimilars could actually be more expensive than brands once beneficiaries reach the gap.

OPPORTUNITIES FOR CHANGE AHEAD?

Biosimilar developers see an opportunity to address some of the reimbursement disincentives created by CMS in the new political environment.

Biosimilars represent "big-time, long-term investments and I think the current reimbursement structure that CMS has proposed does not reward that," Boehringer Ingelheim GMBH Associate Director Public Policy-Biosimilars, Pipeline, Reimbursement Molly Burich commented during the FDA/CMS Summit Dec. 14.

"I wish the provisions" establishing the biosimilars pathway within the 2010 Affordable Care Act "were a bit more clear in terms of how biosimilars should be viewed in terms of being single source products," Burich said. "I'd want to fix the reimbursement piece because in 2010 we didn't know how ... CMS would view it, but also we didn't know how complicated this was going to be."

Co-panelist Kimberly Greco, Amgen Inc.'s director of global regulatory and research and development policy, said she "couldn't agree more. ... We believe that the framework that CMS has laid out actually really discourages engagement in the development of biosimilars and it's sort of a short-term thinking from our perspective." ▶

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Wellcome Trust Makes AMR Strategic Priority After Funding O'Neill Review

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Wellcome Trust – the second largest charitable foundation in the world and co-founder of Human Genome Project – has made drug-resistant infections one of its strategic priorities and plans to use its political independence and financial power to maintain momentum built by the UK's O'Neill AMR Review, which it co-funded, according to the trust's policy head Ed Whiting.

The decision to make antimicrobial resistance a strategic priority was formally taken at the end of 2016 by the board of Wellcome Trust, which uses its £20.9 billion investment portfolio to, among other things, fund innovative science. The decision encompasses more active policy participation and direct engagement with pharma industry stakeholders on issues such as incentives for antibiotic development. The organization is second only to the Bill & Melinda Gates Foundation in terms of large charitable groups.

"Wellcome Trust will be playing a significant role in the future on drug resistant infection. What we want to do is ensure the link between basic science and more programmatic funding is made, so when there are advances in basic science – which we fund an enormous amount of – you can then connect those, to work on drug discovery, such as new antibiotics, and also make sure we're applying the best possible disciplines, for example in surveillance, and the use of data, and understanding best ways to share burden loads, particularly in developing countries," Whiting said in an interview.

Whiting, who joined Wellcome Trust last August, was previously private secretary to former UK Prime Minister David Cameron and had worked with Lord O'Neill of Gatley – the ex-chair of Goldman Sachs Asset Management and the man appointed by Cameron to launch and chair a review into the crisis of antibiotic resistance, the last of which was published in May 2016.

"We want to get much more active, much more visible. And we also want to help policy co-ordination more than we have in the past."

*Ed Whiting, Wellcome Trust's
Director of Policy*



Photo credit: Wellcome Trust

The Review on AMR – which warned that by 2050 a drug-resistant infection will kill someone "every three seconds" unless we act now – was jointly supported by the UK Government and Wellcome Trust, although operated with full independence from both. Established as a two-year, time-limited process, the review engaged widely with international stakeholders to understand and propose solutions to the problem of drug-resistant infections from an economic and social perspective.

That UK-sponsored initiative culminated in a high-level UN meeting last September which saw all 193 member countries sign a declaration in which they pledged to take concrete action on tackling antimicrobial resistance. That followed from the G20 communique earlier that month in which the world's richest countries promised to promote prudent use of antibiotics and called for options to tackle AMR.

The UN declaration called for a coordination group on this work between the WHO and UN, in order to drive action and report back on progress in two years' time. How that will work has not yet been announced, but this is a major step in working across international borders and gaining some real traction on this work.

To help maintain that momentum, the Wellcome Trust has decided to raise its

profile and activities seeking ways to tackle AMR. The charity has, since early 2016, been conducting analyses and working with stakeholders and partners to better understand the gaps in knowledge, practice, resource, research and action related to the AMR crisis. It has mapped out the trust's past investments related to drug-resistant infections – totaling nearly £300m – and the impact that that funding has had. It's now developing a plan to move strongly forward to help tackle the problem.

"We want to get much more active. Much more visible. And we also want to help policy co-ordination more than we have in the past," Whiting said.

O'NEILL REVIEW WAS STEP TOWARD MORE ACTIVE POLICY PARTICIPATION

That reflects recognition that with the O'Neill Review the trust took a big step towards making active policy proposals.

"In the future, we have many different organizations – civil society and governmental and intra-governmental organizations – making proposals about what they'll do about AMR, but there is a need for as much policy co-ordination as we can manage. So we're looking at how the Wellcome Trust can do that and how it can support the WHO and their work and

the process of producing national action plans on AMR and how we can add value in bringing scientists and experts together and using the funding that we can give out to support both reduction in the current use of antibiotics but also increasing access to antibiotics in countries where that is difficult.”

“It’s clear that both governments, private funders and so on will need to think again about how they pay for antibiotics, but also that industry will need to think as creatively as it can about the payment structure.”

To that end it helped launch a new transatlantic partnership to tackle the growing threat of drug-resistant infections. The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) brings together leaders from industry, philanthropy, government and academia. CARB-X, based in Boston, Massachusetts, is possibly the largest public-private partnership in the world dedicated to preclinical antibiotic development. It involves seven partners in the United States and the UK, and it is backed with half a billion dollars in funding. CARB-X partners are working together to set up a diverse portfolio with more than 20 high-quality antibacterial products.

“The thesis of CARB-X is around early

stage drug development,” Whiting explained, noting that the US Biomedical Advanced Research and Development Authority (BARDA) usually enters drug development funding at a relatively late stage. “They were realizing that we weren’t seeing the volume of interesting and innovative early stage clinical trials –

Phase I and Phase II. CARB-X is an initiative to get them working with us in the early development space so we can bring forward exciting new candidates and have a pretty open application process internationally so we can really try to identify where are the really most interesting, most innovative potential drug development candidates, how we can deduce that and how we can pull them through the development cycle quicker.”

He said that over time that R&D alliance “will look at how we can learn from and apply it to diagnostics, and also ensure that we can apply firm standards of access to drugs so that we can get drugs out quickly.” The final AMR Review by O’Neill recommends that it should be manda-

tory for all antibiotic prescriptions to be informed by a diagnostic test (where one exists) by 2020. “We will eventually need to look at diagnostic tools and how we can increase the availability of affordable diagnostics across the world so that we can ensure that antibiotics are only used when they are needed,” Whiting said.

Wellcome Trust will also actively engage in the dialogue with the pharma industry to come up with new proposals for “pull” economic and investment incentives outlined in the O’Neill Review to allow the world to pay for new antibiotics in a viable way that also provides the adequate incentives for drug manufacturers.

O’Neill, in an earlier interview, warned the globalized drugs industry it needs to play ball and help find a solution to antimicrobial resistance or risk getting blamed for its failure and the resulting world health crisis.

Whiting agreed, adding: “This is not going to work if we don’t produce the antibiotics and don’t find an effective way to pay for it. It’s clear that both governments, private funders and so on will need to think again about how they pay for antibiotics, but also that industry will need to think as creatively as it can about the payment structure. How much de-linkage is industry willing to allow? That must also be determined, and rather soon.” ▶

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ADVISORY COMMITTEES

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Neurocrine Biosciences’ valbenazine for tardive dyskinesia	Psychopharmacologic Drugs	Feb. 16 CANCELLED
Pediatric-focused safety reviews for various products as mandated by the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act; role of pharmacogenomics in pediatric product development	Pediatric	March 6-7
Strategies, approaches and challenges in model-informed drug development, including use of physiologically-based pharmacokinetic modeling and simulation throughout a drug’s life cycle and mechanistic model-informed safety evaluations	Pharmaceutical Science and Clinical Pharmacology	March 15



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FDA's NDA And BLA Approvals: Caspofungin

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				
Fresenius Kabi	Caspofungin acetate	Injectable echinocandin antifungal for empirical therapy for presumed fungal infections in febrile, neutropenic patients; treatment of candidemia and the following Candida infections: intra-abdominal abscesses, peritonitis and pleural space infections; treatment of esophageal candidiasis; treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies	S, 5	12/30/2016
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		

This week the Recent and Upcoming Advisory Committee Meetings are on p. 20.

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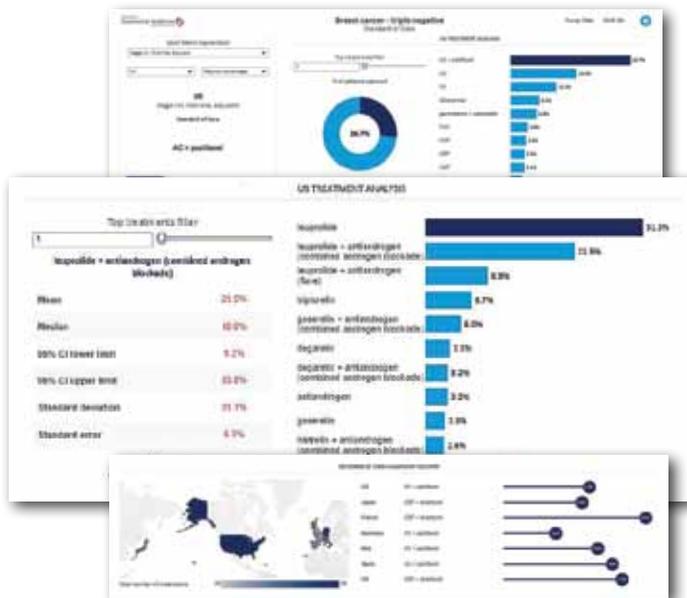
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