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FDA User Fee Hearing Hijacked By US Health Care Reform Arguments

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Democrats used a Senate hearing on the US FDA's user fee program to attempt to reframe the drug pricing debate, arguing that the GOP's plan to speed generic approvals may not be enough to drive down prices.

While Republicans have held up the generic drug user fee program as an answer to increasing drug prices, namely because it can create more competition for high-priced brand and single-source generics, Sen. Patty Murray, D-Wash., contented that it may not be the only solution necessary.

During the March 21 Senate Health, Education, Labor and Pensions Committee hearing on the four user fee programs, which are up for reauthorization this year, Murray asked Center for Drug Evaluation and Research Director Janet Woodcock how many of the approximately 2,300 generic drug applications under review would enter a new or existing market with no other competition.

Woodcock answered that six first generic applications are held up by patent expiry and that another nine would enter sole-source markets, where there is only one sponsor marketing the product, but no blocking patents.

Murray said that was not very many, and Woodcock admitted "that doesn't address the entire problem."

> Sen. Murray suggested that increased generic competition alone is not the solution to drug price concerns.

"But I must stress that the second generic drug user fee program has many features," Woodcock added. "It is intended to move these along as much as possible." GDUFA II includes a priority review pathway for first generics and sole-source products that would be faster than the standard 10-month review goal. *(Also see "ANDAs Can Get Priority, Eight-Month Reviews Under User Fee Deal" - Pink Sheet, 24 Sep, 2016.)*

FDA has also been working on other ways to encourage development of generics for complex products that currently don't have competition, and the effort could be a particular focus for FDA Commissioner nominee Scott Gottlieb, but it seems unlikely that opening that spigot would be able to wash drug pricing concerns out of the public's conscience entirely.

Murray took Woodcock's answer to suggest that more may have to be done to deal with drug pricing. During the exchange, Murray indicated her support for legislation that would allow CMS to negotiate drug prices paid in the Medicare Part D program. "I think it's pretty clear that this agreement will make some important improvements to the generic drug approval process, which I support, but it alone is not going to solve [the drug pricing problem]," she said. "We're going to have to do the work outside this to make that happen."

One area that does not need adjustment relates to combination products. Woodcock and Center for Devices and Radiological Health Director Jeff Shuren said that they do not need a separate approval pathway for combination products.

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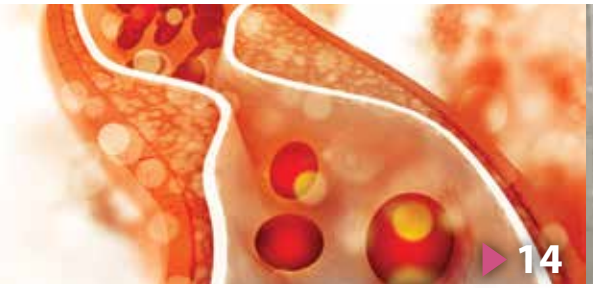
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UK Orphan Drug Access Slammed; Shire Calls For Urgent 'Access Summit'

http://bit.ly/2mZ29va

Orphan drugs "are falling through the cracks" of the UK's market access process, Shire's country general manager tells the Pink Sheet and calls for urgent all-party remedial talks.

Korean Pharma Calls For New Policy 'Control Tower', More Support

http://bit.ly/2odGGzP

Amid the recent ousting of President Park Geun-hye amid corruption allegations and a new presidential election only weeks away, the South Korean pharma industry is quickening its calls for policy support from the next administration by recommending a variety of changes.

The Freeze Thaws: US FDA Allowed To Hire Staff For Cures, User Fee Activity

http://bit.ly/2nPUiFj

White House allowed agency to hire some new employees, but lawmakers remain concerned about federal hiring freeze's effect on FDA.

Combo Products Won't Get Special Review Pathway At US FDA Anytime Soon

http://bit.ly/2nbL8j9

Jeffrey Shuren and Janet Woodcock tell Senate committee that agency is more concerned with implementing combination product provisions of the 21st Century Cures Act.

100% User Fees For US FDA? Trump Budget Revives Important Issue For Industry – But Not This Year

http://bit.ly/2nMamaV

Trump Administration's surprising call for increased user fees probably won't have much impact on pending reauthorization process, but it does put on the table an important question for the biopharma industry to consider for the long term: should FDA be fully funded by user fees?

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A NEW PRICING WRINKLE

REMS reform may be making progress, at least symbolically, as one part of solution to the pricing problem. At the first Congressional hearing on user fees this cycle, Republicans didn't talk about the issue at all. At this hearing, Sen. Susan Collins, R-Maine, brought up abuse of Risk Evaluation and Mitigation Strategies to keep generics off the market during the hearing.

But Collins' preferred solution to REMS issue is not one that the generic industry feels is adequate. She is the Senate sponsor of legislation also introduced in the House that calls for a Government Accountability Office report on the issue of REMS blocking generic development and approval. ANDA sponsors feel the issue has been studied enough, and support legislation that prevent the programs from denying access to samples or a path through FDA for generic versions.

The legislation also would make sponsors of sole-source and other generics eligible for a priority review voucher, but those elements haven't exactly been embraced by industry either. *(Also see "Bill To Speed ANDA Approvals Gets Cool Reception From Industry, US FDA" - Pink Sheet, 2 Mar, 2017.)*

While Collins has explored the REMS issue in the Senate Aging Committee, which she chairs, Republicans largely have shied away from suggesting fixes to the REMS system to encourage faster generic entry.

The House Oversight and Government Reform Committee also will conduct a hearing March 22 on restrictive drug distribution programs. But no House Republicans asked about the issue during the House Energy and Commerce Subcommittee on Health hearing on generic and biosimilar user fee reauthorization at the beginning of the month. *(Also see "REMS Reform Seems Distant Goal For Generics After Limited Support At US House Hearing" - Pink Sheet, 2 Mar, 2017.)*

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Combo Products Won't Get Special Review Pathway At US FDA Anytime Soon

The hearing might be a sign that the issue is gaining strength as a drug pricing fix, even though brand companies historically have opposed making the changes. *(Also see "GPhA Pushes REMS Pay-for, Schedule III Hydrocodone In User Fee Bill" - Pink Sheet, 6 Jun, 2012.)*

> Several committee members connected FDA to the Republican health care reform effort, saying that faster drug approvals will not make much difference to those who could lose insurance coverage under proposed ACA changes.

Republicans in the House have consistently argued that by allowing more generic drugs and biosimilars on the market, prices will come down. During the House hearing, they spent a lot of time asking Woodcock about whether allowing more pre-submission meetings would help speed generic approvals. *(Also see "US Generic Reviews: Would Pre-Submission Meetings Be Better Than Six-Month Priority Review?" - Pink Sheet, 5 Mar, 2017.)*

FDA CAUGHT IN ACA REPEAL COMPLAINTS

Democrats also used the hearing to complain to committee Chairman Lamar Alexander, R-Tenn., that its topic should have been the House's legislation repealing and replacing the Affordable Care Act, which could arrive at the Senate in the coming days and potentially move straight to the floor.

Once the hearing was scheduled, all Democratic members of the committee signed a letter asking that the topic be ACA reform instead. But Alexander said the user fee bill also deserved the attention.

"The authority for FDA to collect user fees for medical product review will expire on September 30 of this year – six months from now," Alexander said. "If we do not move quickly to reauthorize these agreements, in late July, the FDA will be forced to begin sending layoff notices to more than 5,000 employees to notify them that they may lose their job in 60 days. A delay in reauthorizing these agreements would delay the reviews of drugs and devices submitted after April 1."

Throughout the hearing, Democrats used their time for questions to complain that the House's American Health Care Act would not be considered by the committee before reaching the floor. Sen. Christopher Murphy, D-Conn., used all of his time complaining about the issue. At the end of his statement that he had no questions for the FDA officials at the hearing.

Several members also connected FDA to the Republican health care reform effort, saying that faster FDA drug approvals will not make much difference to those that could lose insurance coverage under the proposed ACA changes.

"If the Republican bill to gut American health care becomes law, all the miracle cures and speedy FDA approvals in the world won't matter to the tens of millions of Americans who won't be able to afford them when they get sick," said Sen. Elizabeth Warren, D-Mass.

The HELP Committee plans another user fee-focused hearing, likely April 4, to hear the perspective of patients, drug manufacturers and others on the reauthorization agreements. Lawmakers want to finish the package by July to avoid forcing FDA to tell affected staff they may be laid off if the programs are not reauthorized by their expiration in October.

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Now Is The Time! Rule Changes To Smooth China New Drug Approvals?

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Spring may finally be here for multinationals looking for a smoother development path for their new drugs in China.

Just days after the head of the country's drug review and approval agency expressed publicly a willingness to welcome more foreign drugs into China, a new draft regulation that promises just that has been released by the China FDA.

The document, dated March 17, proposes revising a burdensome requirement relating to the conduct of multi-regional clinical trials (MRCTs) at sites in China and potentially allowing the more simultaneous conduct of early-stage studies in the country. [Link to CFDA Draft Adjustment to Imported Drug Registration Requirement – Chinese language].

The purpose of the revision, per the CFDA, is "to encourage novel new drugs that have not yet been approved overseas to conduct parallel studies in China upon [study] approval, to shorten the new product [approval time and] launch lag between inside and outside China, and to meet the public demand for new drugs.

FOUR MAIN POINTS

There are four main points mentioned by the CFDA in its draft document, all of which look positive for the foreign pharma industry and the commercialization of new drugs in China.

The first concerns the elimination of the current requirement that a new drug for which an MRCT is planned in China must have been approved - or at least have entered Phase II or III trials - in another country overseas. Vaccine products are the exception.

Additionally, the draft proposes that upon completion of the MRCT in China, a new drug application can be filed with the CFDA directly using the data obtained from the study (rather than any other additional Chinese studies), although the NDA will need to comply with the requirements of China's Drug Registration Administration and other rules.

A third planned change is to eliminate a requirement for a certificate of pharmaceutical product for imported chemical drugs and biologic products. This has had to be issued by the competent authorities of the country where the manufacturer is located and should comply with World Health Organization format, and has been used as an additional way to ensure safety and quality,

Finally, for MRCT applications that have previously been filed and accepted, the CFDA will grant a waiver for any additional local trials on condition the filings meet the other new requirements. (Applicants have usually had to apply separately for this waiver.)

TWO TO THREE YEAR SAVING?

The new moves are a direct departure from the CFDA's previous "*Sanbaosanpi*", the so-called three filings, three approvals procedure for new imported drugs due to the different levels of requirements, which has been in place since 2014 but is generally considered burdensome by applicants.

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CFDA PROPOSALS TO STREAMLINE MRCTS

- Drugs do not need to be approved overseas or to have entered Phase II or III trials in another country;
- Data from MRCTs can be used for China NDA filings;
- Imported drugs will not need CPPs; and
- Trial waiver will be granted for previously filed MRCTs.

This system usually requires an MRCT application, plus a filing to conduct local trials, and then the final NDA to secure approval. Pre-2014, applicants conducting completing MRCTs could apply for a waiver for local-only trials, but the Sanbaosanpi system effectively did away with this, added an extra procedural requirement for a local clinical trial approval.

Multinationals have complained that the additional requirements for the conduct of clinical trials with new drugs in China have delayed new product launches by an average of around 30 months, or 2.5 years

The new revisions, if implemented, could therefore be significant for companies eager to launch their novel products in China, noted one veteran clinical study manager working for a multinational pharma firm in China.

"There are two aspects to the issue. One is that a clinical trial approval would be accelerated, allowing study sponsors to include China study in a parallel global study. And secondly, the data ob-

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Foreign Drugs Welcome As China Reforms Progress: CFDA Commissioner
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Additional approval requirement in China pains drug industry
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tained from the study will be able to be used towards a NDA filing; both are important," he told *Scrip*, adding there could be a two-year shortening in the current delay for new product launches in China.

One legal expert agreed. Katherine Wang, a partner at law firm Rope & Gray's Shanghai office, said the changes would benefit obtaining both clinical trial approvals and NDAs for imported drugs in China.

"It appears to revise the course [back to prior to 2014] when data from MRCTs could be used directly towards a product approval filing, and on top of that, the rule further relaxes requirements for imported drugs applying for clinical trials approvals, which would be a good news if implemented," said Wang.

INNOVATION, ACCESS

Both the industry observers said the draft rule could potentially spur earlier stage Phase I work in China, which bodes well for the government's plans to switch to an innovation-driven economy and encourage original research.

In a note on the changes, Jefferies analyst Eugene Huang said the changes could cause MNCs to refocus on China, and might bring new work and pricing opportunities to contract research firms as sponsors look to more local studies to access large patient pools, save costs, and build links with local researchers.

On the other hand, domestic generics firms might be hit by a closing of the drug lag, and perhaps by a lowering in local development costs that might enable more price reductions by foreign firms.

Interestingly, the new move came after China's recent annual plenary *Two Sessions* meetings (of the People's Congress and Political Consultative Meetings), during which CFDA Commissioner Bi Jinquan said the country welcomes more foreign drugs. *(Also see "Foreign Drugs Welcome As China Reforms Progress: CFDA Commissioner" - Pink Sheet, 15 Mar, 2017.)*

It also came ahead of a high-level discussion forum in which several global pharma CEOs were due to discuss their ideas with Chinese leaders on topics ranging from regulatory reforms to innovation ecosystem building. *(Also see "Big Pharma CEOs Descend On China: What's The Likely Agenda?" - Scrip, 17 Mar, 2017.)*

RECENT APPROVALS

There have been other positive signs over new drug access as well. Just two days ahead of the release of the new CFDA draft proposals, the regulator approved **Pfizer Inc.**'sJAK inhibitor *Xeljanz* (tofacitinib) for rheumatoid arthritis, along with several other new drugs from multinationals granted recent nods. These included **AstraZeneca PLC**'s *Forxiga* (dapagliflozin) for type 2 diabetes and afatinib from **Boehringer Ingelheim GMBH** for non-small cell lung cancer.

"We applaud the efforts of the Chinese government and the CFDA to bring new medicines to the Chinese healthcare system," Pfizer China country manager Wu Xiaobin said in a statement. The Xeljanz approval was based on efficacy and safety data obtained from a global study with a subgroup in China, the company noted.

Public comments on the draft CFDA proposals are being collected until April 20 via www.chinalaw.gov.cn and email submissions can be made to: hxypc@cfda.gov.cn with the subject "Adjustment to Imported Drugs Opinions."

From the editors of PharmAsia News. Published online March 21, 2017

UK BioPharma Players Told 'Think Global, Act Local' For Post-Brexit World

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UK BioPharma movers and shakers met recently at **AstraZeneca PLC**'s Macclesfield manufacturing plant in Northwest England where they were told to join up efforts and to 'think global, act local' in the coming post-Brexit era if they want to ensure their sector keeps its prominent place within the British economy and continue to thrive internationally.

The Mar. 20 event was headlined as an update on efforts to promote the UK as a place for medicines manufacturing and to identify new ways to retain and attract the making there of advanced therapies.

But the discourse quickly turned to a collective biopharma overview – and an overall message for the need for all active parties - spanning biopharma companies, input suppliers, government, regulators and end-users – to collaborate much more openly to "develop connective tissue" across the sector's research and development and production systems.

'IT'S GOOD TO TALK'

In the absence of a clear roadmap – Brexit negotiations between the UK government and the European Commission have yet to begin - some participants at the Macclesfield meeting suggested a wide-ranging Davos-style UK national forum of key opinion leaders and decision makers might prove useful, where "blue sky" discussions on future trends and disruptive issues could take place. Such forum discussions would be invaluable for collabora-

tion and co-operation given the constantly changing nature of the biopharmaceuticals industry and world geopolitics. Such meetings might even include players from different industries who also face huge technological change and Brexit uncertainties, such as aerospace or specialist chemicals, one CEO panelist suggested.

The importance of the life sciences sector to the UK economy was underscored by ABPI chief executive Mike Thompson, who noted from the stage that "our industry contributes around £30bn to the British economy and there's a head office of a UK life sciences firm in every region of the UK." Meanwhile the UK's pharmaceutical manufacturing sector generates impressive productivity levels, 40% higher than Germany and Italy, 50% higher than Spain, and nearly twice that of France, according to the ABPI.

Richard Turner, a managing director at FTI Consulting, told the grouping that Britain also offers one of the most competitive tax and fiscal frameworks for medicines manufacture in the world, combining low tax rates, innovation incentives such as R&D tax relief and the so-called Patent Box granting a favorable tax rate of 10% on profits attributable to UK patents. But he said further steps could be taken to bolster competitiveness, including fiscal policies that promote the manufacture of new therapy areas such as cell and gene therapies.

MMIP MODEL

One on-going collaborative initiative discussed at the meeting - and which is experiencing some success - was the Medicines Manufacturing Industry Partnership (MMIP). It was established jointly by the British government and the biopharmaceutical industry in 2014 to give a collective voice to UK-based medicines manufacturers and identify ways for the sector to jump to the next generation of medicines and ensure the UK remains an early adopter of manufacturing and delivery innovations. In its efforts to do so, the MMIP also works with government organizations such as the Medicines and Healthcare Products Regulatory Authority (MHRA), the UK Trade and Investment department (UKTI), Innovate UK, and the Office for Life Sciences.

> "In our view a 'red line' has been crossed." – ABPI CEO Thompson commenting on new NICE and NHS England drug access and reimbursement appraisal rules

Speakers voiced optimism that the UK government has identified the life sciences sector as a key part of the economy that needs nurturing - a message reinforced by Lord Brampton, minister at the Department for Business, Energy and Industrial Strategy with responsibility for the sector. He told the meeting that the Conservative government is coming around to the view that an activist technology policy and government backing for important economic sectors will be crucial going forward. He said successive governments got it wrong in the past when it came to navigating technological change and adapting UK worker skill sets to those changes in order to cushion the impact on the country's labor force and the overall economy. "We did incredibly badly in the 1980s - and it's something we've got to do a lot better," Lord Brampton added.

But to do so, certain recent trends need reversing.

Over the last decade, many large biopharma companies have cut the number of people that they employ in in-house discovery in Britain while increasing their R&D activities in the US and Continental Europe as well as new markets in Asia, according to the ABPI.

Still, encouraging signals have come from the UK government, which is currently formulating its industrial strategy. There is spreading optimism that life sciences will be at its core – a view bolstered by the government's Autumn Statement presented last November which contained an unexpected multi-billion-pound increase to R&D funding so that by 2010 government spending on research and development will be £2bn more than it is today, at a targeted £4.7bn.

Lord Prior of Brampton said that reflected the spreading view that industrial strategy answers will not result from incremental strategy approaches. "We need to have a strong industrial strategy… And if we are going to move ahead on these things we're not going to do it by increasing spending on research by 3% or 5%. We're going to change it by doubling it, or quadrupling it, or multiplying it by ten if we're going to make a difference. But this will require us to make some difficult choices," he said.

BUMPS LIKELY – 'RED LINE' CROSSED

There will be bumps along the way – a point noted by APBI CEO Thompson, who took time during the meeting's panel discussions to condemn the latest rules changes by the UK HTA, NICE, telling the gathering that "we all know that the UK, the NHS and the industry all face huge challenges … but it would be disingenuous not to mention the NICE board decision last week," he said. *(Also see "NICE Appraisal Changes: Confusing, Contradictory & Questionable" - Pink Sheet, 17 Mar, 2017.)* "We see these as breaking the [Conservative Party] government's manifesto and patients' rights to receive cost-effective medicines," he said.

"In our view a 'red line' has been crossed," he added.

"To work, an industrial strategy needs to be 'end-to-end'. Critically these proposals are likely to adversely affect first-in-class innovations that improve the health of the most patients. And clearly that is completely at odds with the UK's industrial strategy proposition of setting out this country's stall as a global innovation hub. If people had been working together in a way similar to that of the MMIP, then there would have been found a solution to this. But we haven't. "

From the editors of PharmAsia News.
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US FDA Pushing For Generic Alternatives To Long-Acting Injectables, Implants

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The US FDA anticipates that new research will provide more insight on the processes used to manufacture long-acting polymer based implants and injectable drugs in order to spur generic drug development. Officials are concerned that the complexity posed in manufacturing these drugs is delaying the development of generic alternatives.

Called PLGA (polylactic co-glycolic acid) these are biodegradable polymers which are key components of long-acting release drug products. PLGAs can be formulated into microspheres, in situ forming gels and implants.

These concerns about the lack of generic availability of these drugs were aired at a recent joint FDA and US Pharmacopeia workshop on standards for pharmaceutical products in Rockville, Md. The workshop explored the issues with manufacturing complex generic drugs such as topical drugs, inhalation drugs, and parenteral drugs using PLGA-delayed release mechanisms.

At the meeting, members of the academic community discussed some of the PGLA research being conducted to study the influence of raw materials, manufacturing variables and storage conditions of long-acting injectable microsphere products.

The issue of how to how to speed generic entry into the market has taken on renewed salience as the drug pricing debate has heated up in the US, and FDA Commissioner nominee Scott Gottlieb could make it a signature issue. *(Also see "Gottlieb Nomination As US FDA Chief Could Signal Changes To Generic Approval Process" - Pink Sheet, 13 Mar, 2017.)*

FDA officials said that PLGAs are currently used in 15 approved products to treat a variety of diseases. They include the following products:

- **Implants:** for treatment of macular edema, (*Ozurdex*) and prostate cancer (*Zoladex*);
- **In situ forming gels:** for treatment of periodontitis (*Atridox*) and advanced prostate cancer (*Eligard*);
- **Microspheres:** for treatment of endometriosis (*Lupron*), advanced prostatic cancer (*Lupron Depot*), central precocious puberty (*Lupron Depot-PED*), advanced prostate cancer (*Trelstar*), schizophrenia and bipolar 1 disorder (*Risperdal Consta*), alcohol dependence (*Vivitrol*), type 2 diabetes (*Bydureon*), acromegaly for subcutaneous administration (*Sandostatin LAR*), periodontitus (*Arestin*), gastroenteropancreatic neuroendocrine tumors (*Somatuline Depot*) and acromegaly for intramuscular administration (*Signifor LAR*).

Steven Schwendeman, a professor of pharmaceutical sciences at the University of Michigan, said that a number of these drugs "are hot" for generic development including Lupron Depot, Risperdal Consta, Vivitrol and Sandostatin LAR. Yet he said it is very difficult and costly to establish equivalency for these drugs because of the complex nature of the material properties of the polymers used in formulations.

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FDA awarded a grant to the University of Michigan to help bridge the knowledge gap for PGLA products and to aid the agency in developing guidance on equivalence determinations for these products.

OGD INITIATIVES TO SPUR GENERIC DEVELOPMENT

FDA's Weinlei Jiang, senior science advisor with the Office of Generic Drugs (OGD), said that one challenge is characterizing the polymers in PGLA drugs. Polymers in these drugs can be either be naturally derived or synthetic and it can be difficult to characterize them because they degrade.

She said that "in some cases you have to do reverse engineering on the polymer. However this can be a challenge because the polymer may have already degraded."

Stephanie Choi, the acting associate director for science at OGD's Office of Research and Standards, described some of the initiatives being undertaken at OGD to spur the development of complex dosage forms, including long acting release drugs.

She said that FDA recognizes that complex products need different approaches for demonstrating equivalence compared to more traditional solid oral dosage drugs that do not have novel delivery mechanisms.

Choi said that the agency is busy issuing product-specific guidance dealing with these different drug formulations and has so far issued seven product specific recommendations for microsphere

products to provide guidance on bioequivalence study design.

Also under GDUFA II, makers of complex drugs will be able to request presubmission meetings to discern potential problems before ANDAs are submitted. The complex products pre-ANDA program is reserved for a small number of ANDAs, such as those with complex active ingredients, formulations, routes of delivery or dosage forms, or complex drug-delivery combinations *(Also see "Complex ANDAs To Be Allowed Pre-Submission Product Meetings" - Pink Sheet, 24 Oct, 2016.)*.

Choi said that FDA is also soliciting the help of outside groups to develop more tailored policy on complex generics. A provision in the 2012 Generic Drug User Fee Amendments (GDUFA) allowed user fees to support regulatory science research activities to expand access to generic versions of complex products through the use of different in vitro bioequivalence approaches. GDUFA's regulatory science program supports development of generic drugs in all product categories, including inhalation and nasal drugs, topical dermatological drugs, ophthalmic drugs and sustained release parenteral drugs.

Choi said that since 2013 OGD has awarded grants for multiple research projects involving PLGA based drug product in various dosage forms, such as microspheres, implants and in situ gelling systems. These projects can be categorized into four areas: developing in vitro in vivo correlations (IVIVC), developing in vitro release test methods, characterizing PLGAs and modeling and simulation of PLGA based drug products.

The University of Michigan was awarded two grants, one in 2013 to study IVIVD correlations of parenteral microsphere drug products and another in 2015 to characterize PLGAs and to study the influence of raw materials, manufacturing variables and storage conditions on release of long acting injectable microsphere products.

DIFFICULTIES WITH POLYMERS

Schwendeman said that there are major advantages to PGLA based drug products in terms of the delayed release dosing.

He said that "for Lupron Depot used in cancer patients you can go from once a day injections to twice a year injections. This is only possible because of these biodegradable depots, this is a dramatic improvement in the lifestyles for these patients." He focused his remarks on developing PGLA microspheres.

Yet there are multiple challenges in manufacturing PGLA products not the least of which is the cost and the time to develop them.

He explained that it is expensive to manufacture the polymers because it involves many processing steps involving multiple unit operations and at low yields. These products also require aseptic processing, which is expensive. Also the proteins used to make the polymers are unstable and the assays for these products do not exist.

Another barrier is that there is a lack of understanding of what governs the difference between in vitro release assays and in vivo assays.

Schwendeman said that to try to mimic a RLD and develop a generic platform and that "to develop the infrastructure to do that we have to reverse engineer and for an academic lab this is a fair amount of work."

He said that the nature of polymer chemistry is also challenging because it involves a wide area of disciplines, so it is important for pharmaceutical manufacturers to have a team with broad expertise working on these products, such as biopharmaceutical classification, materials science and analytical chemistry.

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Australian Provisional Approval Pathway To Get Tough On Sponsors Upfront

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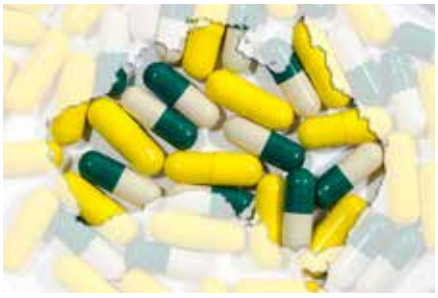
Australian regulators developing a provisional approval pathway for drugs plan to be tougher on drug sponsors upfront compared with similar schemes elsewhere in a bid to avoid the problem of companies failing to fulfil the post-marketing conditions of their registration on time.

Provisional approvals will not be granted unless applicants can prove to the Therapeutic Goods Administration that they will be able to collect the necessary confirmatory data within the provisional registration period, the agency says in a second round of consultations on the pathway.

The provisional approval pathway is an early access scheme that the TGA is developing to bring domestic practices into line with the likes of the EU, US and Canada. It will allow certain medicines for unmet clinical needs to reach patients up to two years earlier than usual, based on fewer – or different – clinical data than would normally be required. Sponsors would need to collect and submit post-market safety and efficacy data before a decision is made about whether to grant the product full registration.

Experience of similar pathways abroad has shown there can be delays with sponsors fulfilling registration conditions to submit



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data from post-registration studies, the TGA notes, highlighting the European Medicines Agency's conditional marketing approval (CMA) as an example. Delays in meeting post-marketing requirement in the EU has in

the past sparked concern that the CMA was being used inappropriately and that companies were being given permission to extend their deadlines or change their obligations. *(Also see "EU Conditional Approval Should Be A Drug Development Tool, Not A Rescue Remedy" - Pink Sheet, 2 Jun, 2016.)*

The TGA wants to make sure that sponsors conduct the clinical trials needed to generate the confirmatory data that were agreed on as part of their provisional approval. It is proposing only to grant a provisional registration on the condition that sponsors can demonstrate their ability to collect and submit the efficacy and safety data that would normally be required for full registration during the provisional registration period.

Sponsors should be able to provide evidence that planned clinical trials will be completed within the provisional registration period, taking into account the possibility of future extensions. For example, they may provide evidence that the trial is fully or almost fully recruited prior to registration, or that the data can be obtained through another mechanism that is deemed suitable by the TGA (such as the same treatment regime in a similar population group).

According to the consultation document, sponsors would need to address potential barriers to the collection of data as part of their provisional approval application process, and outline the steps they have taken to overcome them.

REGISTRATION AND TWO-YEAR DEADLINE

Last October, the TGA consulted on the eligibility criteria and designation processes for the pathway. *(Also see "Australia Consults On 150-Day Priority Review, Provisional Approval" - Pink Sheet, 31 Oct, 2016.)*

The latest consultation document, issued on March 20, is seeking feedback on proposed provisional approval registration processes, post-market requirements, and on the provisions covering lapsing approvals and transitions to full registration.

The document says that early clinical data used to support a provisional approval application could be based, for example, on fully validated surrogate endpoints or other early data relevant to the medicine's safety and efficacy, rather than comprehensive data from Phase III clinical trials.

Applications would have to include comprehensive quality and non-clinical safety modules that fulfil the TGA's mandatory data requirements. The agency notes that pivotal or supporting clinical trials are likely to be ongoing during the pre-market registration period.

"On a case-by-case basis, the TGA may agree upfront for the sponsor to make a rolling submission of clinical or other relevant data during the assessment period, where this information might have a material impact on the registration decision," the consultation document says. "However, this approach could lead to inefficiencies and potential delays if aspects of the evaluation needed to be revised to account for the additional data. In order to facilitate evaluation planning and TGA resourcing, sponsors will need to prospectively discuss any additional data that will be generated after submission of the dossier and the proposed timeframe for submission."

> A compliance monitoring program is envisaged to check that sponsors comply with activities described in their risk management plan.

The TGA is proposing that the provisional registration automatically lapses at the end of a two-year period, unless the sponsor has applied for full registration of the medicine or the TGA has granted an extension to the provisional registration period. "An extension may be granted by the TGA… for a further period of one or two years, with a maximum of two extensions available to a provisionally registered medicine," the document says. "This proposal will allow for regular review of the efficacy and safety data to support ongoing provisional registration, while balancing resourcing impacts for the sponsor and the TGA."

The TGA says that the sponsor will need to make "a formal Category 1 application, or equivalent" to the agency to seek full registration of the medicine before the provisional registration period lapses.

There are also plans to implement a compliance monitoring program to verify that sponsors comply with activities described in their risk management plan. In addition, the TGA is currently consulting on a proposed enhanced medicines vigilance framework. "This will ensure that the two streams of reform are appropriately aligned and clearly communicated to industry, health professionals and public health advocates and consumers," it says.

"Refusal or failure to comply with a condition of provisional registration may result in cancellation or suspension of registration in the [Australian Register of Therapeutic Goods]," the agency says.

The consultation document also touches briefly on how the reimbursement landscape might be improved so that products that are approved provisionally on the basis of less evidence get reimbursed. "While the MMDR review did not make recommendations about the Pharmaceutical Benefits Advisory Committee (PBAC) processes for PBS listing of medicines, the Government is working to ensure that regulatory and reimbursement processes are appropriately aligned to take advantage of the outcomes of the MMDR reforms," it says.

The provisional approval is one of two new expedited drug approval pathways being developed in Australia as part of the government's September 2016 response to the country's Medicine and Medical Devices Regulation (MMDR) review into how the regulation of medicines and devices could be streamlined. The other pathway is a priority review scheme that could see some novel prescription drugs evaluated within 150 working days. *(Also see "No Delays Expected As Australian Bill On Faster Drug Approvals Goes To Parliament" - Pink Sheet, 2 Dec, 2016.)*

The deadline for submitting comments on the provisional approval pathway proposals is May 1.

From the editors of Scrip Regulatory Affairs. Published online March 21, 2017

NICE Appraisal Changes: Confusing, Contradictory & Questionable

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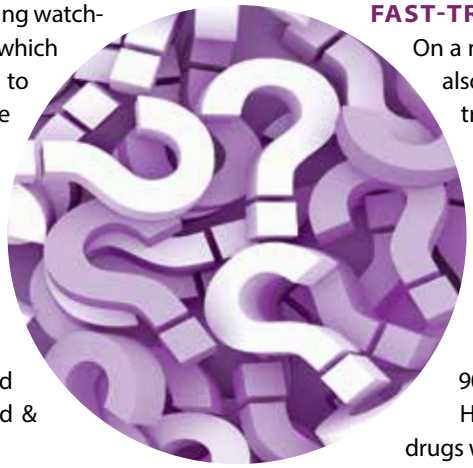
A new "budget impact test" that UK pricing watchdog NICE is introducing in April, which could potentially allow NHS England to delay access to certain drugs by up to three years even though they are deemed to be cost effective, has come under fire.



The test, approved on March 15 as part of a package of changes to the drug appraisal process used by NICE (National Institute for Health and Clinical Excellence), marks an irrational move by the health technology appraisal body and NHS England, said Adela Williams, a partner at law firm Arnold & Porter Kaye Scholer,

Moreover, industry is warning that it is a serious setback for patients that undermines their right to receive cost-effective medicines. It also calls into question whether England remains a viable country in which to invest and launch new therapies.

Under current regulations, NHS England must provide a drug to patients within 90 days of NICE recommending the product shows enough benefit versus its cost for use on the NHS. The budget impact test, on the other hand, will enable NHS England to ask NICE for extra time to negotiate a new price with manufacturers for certain drugs, delaying their use even though they have been deemed cost effective.

Instead of 90 days, NHS England will be able to request up to 1,096 days (a maximum three years) to try to negotiate a new price for drugs that are expected to cost more that £20m a year to the NHS.

It is anticipated that this cost cap will affect one in five new drugs in England. Previously, assessments for novel therapeutics were only assessed on cost versus benefit for individual patients – not by the total cost it may incur to the NHS.

The £20m budget impact assessment is being seen as a second pricing hurdle for companies looking to get drugs to market in England and it also represents a shift in power from NICE to NHS England when it comes to drug pricing decisions. During an extended valuation period, in which time NHS England will invite drug developers to negotiate on pricing for products, NICE will offer phased funding of recommended treatments to patients in England – but this is not a long-term solution and has raised concerns that companies will face pressure to maintain the reduced price after that phase-in time has expired.

NICE will reassess the budget test in three years' time to see what impact it has had on access to new drugs. Last year, £16.8bn was spent on drugs by the NHS, only a small segment of the healthcare provider's total budget for 2016 of £102bn.

FAST-TRACK PLANS

On a more positive note for drug makers, NICE will also introduce next month a scheme for fast-tracking new drugs that have a likely cost per extra year of quality-adjusted life of under £10,000. Drugs that come in under this threshold will be considered "exceptional value for money", the institute said. Under the fast-track option, NHS England would be required to offer the new medicine to patients within 30 days instead of the traditional 90-day deadline.

However, in a contradictory move, fast-tracked drugs will also be subject to the new budget impact test. This means that a product could be granted fast-track status by NICE only to be held up by NHS England if it is likely to create a cumulative bill of more than £20m to the NHS per year due to the number of patients to be treated.

Sir Andrew Dillon, chief executive of NICE, said the budget impact test and the other new changes would "enhance our ability to optimize access to innovative treatments in the light of the significant financial challenge facing the NHS."

The Arnold & Porter Kaye Scholer lawyer, on the other hand, told the *Pink Sheet* that imposing the budget impact test on fast-tracked products was an irrational move by NICE and NHS England. "If you have a medicine that is so cost effective it has a price of less that £10,000 per QALY, then simply because there is a large population eligible for it you shouldn't be able to defer implementation," Williams said.

NICE first announced potential changes to assessment timelines and pricing caps in Oct. 2016. Companies and other parties were offered a chance to comment on the new regulations between Oct. 2016 and Jan. 2017 – but few amendments have been made to the initial proposals.

Another change being introduced concerns medicines for rare diseases. Drugs for very rare diseases will be evaluated against a sliding scale, so that the more the medicine costs the greater the health benefit it must provide in order to be approved for routine NHS use by NICE.

QUESTIONS ON NEW RULINGS

As April nears, several questions have arisen over the new fast-track and budget impact test rules.

How will the budget impact test work in practice?

If a product recommended by NICE has an NHS England budget impact expectation of more than £5m per year, an initial assess-

ment will be carried out to see whether the budget impact expectation is more than £20m. If the budget impact proves to be more than £20m per year, then NHS England can extend an invitation to companies to participate in a commercial negotiation with a view to reducing the impact on funding.

NHS England must justify to NICE why it needs a period of deferral to extend its deadline for providing the product to patients past 90 days (or 30 days if fast-tracked). The length of the extension is likely to depend on how high above the £20m funding cap the original NICE pricing agreements fall when assessed as a total cost to the NHS and not per patient. "In practice, if companies don't agree to a commercial agreement with NHS England that brings the budget impact below £20m we are going to see a deferral and NHS England are likely to argue for as long a deferral as they can because that will give them maximum flexibility," said Williams, who provides advice to clients in relation to pricing and reimbursement issues, including all stages of health technology appraisals by NICE.

When the extension time ends, if no commercial agreement is confirmed with the drug developer, NHS England must then provide the product to patients at the original price agreed by NICE. However, this could be as much as three years later, delaying access to the medicine for patients significantly.

Why are multiple cost assessments needed in England?

It is important to remember that these medicines being assess by NHS England have already been deemed cost effective by NICE. As such, Williams says the extra time granted to NHS England should be used by the organization to make space for the new technology within its budget, as well as to discuss possible price changes with manufacturers.

But if NICE's decisions are not being implemented for up to three years, there is not a lot of point in it issuing guidance on new drugs, Williams commented. "These proposals emasculate NICE to some extent and represent a shift in power towards NHS England that wants to carry out its own determinations for prioritizing treatments," she said.

Rare disease drug developer Alexion, which has experienced arguing for access to the NHS for its highly specialized drugs, told the *Pink Sheet* that these changes to the system are a "serious setback for patients in England suffering from rare and ultra-rare diseases, and for the life-sciences industry in England." The company called into question whether England remains a viable country in which to invest and launch new therapies.

"Alexion questions the Government's commitment to its patients and its pledge to support the life-sciences industry," a spokesperson for the company said. "This decision also puts the UK's Industrial Strategy at risk, which highlighted the life sciences sector as a primary source of innovation for the UK economy going forward."

Industry body the ABPI added that the new plans "will prevent patients from receiving NICE approved, cost-effective medicines, undermining their basic rights under the NHS constitution."

Where did the £20m cap figure come from?

Industry has raised concerns over how the £20m threshold was calculated by NICE and NHS England. After consultation, this query remains unanswered.

Alexion said these changes to the system are a "serious setback for patients in England suffering from rare and ultra-rare diseases, and for the life-sciences industry in England."

Williams said there is no reasoning as to why the cap has been placed at £20m and not another figure. The explanation from NICE in the consultation documents only states that it is a figure deemed reasonable by NHS England and one they can afford. "Frankly, that is not an adequate reason and we should have some greater explanation for why £20m is appropriate as a cutoff point. This has not been explained or been subjected to proper consultation," Williams said.

Datamonitor Healthcare senior analyst Tijana Ignjatovic, who specializes in pricing, reimbursement and market access, also has concerns about how patient numbers will be estimated. "This is not something that NICE does so it will probably be down to NHS England to make some estimates on patient numbers," she told the *Pink Sheet*. "Potentially the manufacturers will have to make their own estimates too in order to be able to predict whether a product's price will place it above or below the threshold."

Are there any differences in the new ruling compared to prior proposals?

Williams noted that the most important and obvious difference from initial plans announced last year by NICE and NHS England is that there is not yet a conclusion about how NICE will address highly specialized technologies. "That section has been shelved and NICE is going to deal with it sometime in the future," Williams said.

There was concern in October and during the consultation period about how the incoming changes to timelines and pricing thresholds would impact treatments for rare diseases, which often have prices higher than NICE's limits. Williams said it is positive that NICE and NHS England are giving further consideration to assessments for highly specialized technologies separately from other new drugs.

However, Alexion, a rare disease company, is concerned about changes to be enacted in April that will increase the maximum QALY threshold for highly specialized medicines from £100,000 to £300,000. Though a higher figure, this option will be restricted only to therapies that provide 30 or more incremental QALYs. "The very high threshold for QALY gains and the strict linkage to the cost threshold is likely to make the new review process even more restrictive than before for therapies targeting rare and ultra-rare diseases," Alexion said. The company claimed that no orphan drugs currently available to patients in England would meet this threshold.

Alexion said it was disappointed in the consultation process for

the new NICE and NHS England regulations. "The responses provided by industry, clinicians and patients advocates on the proposed changes have not been acknowledged or recognized by NICE and NHSE," the company claimed.

What spurred this action from NICE and NHS England?

Ignjatovic noted that the new rules have partially been brought in to reduce a disconnect between NICE's cost effectiveness assessments and the budget impact on NHS England, the budget holder. "NICE only looks at cost effectiveness not at the budget impact so this change may penalize drugs that are very effective and cost effective but target high patient numbers and are likely to be taken up quickly," she said.

However, Ignjatovic added that the ruling was also driven by the large budget impact of hepatitis C drugs in recent years. New hepatitis C drugs provided data to regulators and HTAs showing that the products had impressive cure rates for the disease. This made it hard for pricing authorities in Europe to argue for a lower price because the benefit of the drugs was clearly displayed. While the long-term savings to health authorities of treating hepatitis C patients will be substantial, the initial cost to treat large numbers of patients was seen as too high for healthcare systems like the NHS. These treatments also experienced budget thresholds to limit their costs, but Ignjatovic said the caps on those drugs were not as low as new proposals coming into play from NICE and NHS England that will potentially effect products in all therapy areas.

The budget impact test is NHS England's barrier against another hepatitis C situation, where there were too many patients to treat and the drug prices were set very high, showing that the NHS is fearful of a major breakthrough that it won't be able to afford.

Hilary Evans, CEO of Alzheimer's Research UK, has significant concerns the budget impact test will mean delays for dementia patients accessing any future treatments for their condition. "There is a huge unmet need and with so many people likely to benefit from any new dementia drugs, it is very possible that such treatments may cost more than £20m a year," she said. Evans highlighted that the NHS should be better prepared to budget for breakthrough therapies. "We recognize the funding pressures that currently exist for the NHS, but we believe the budget impact test is not the right tool to fix this complex challenge. The introduction of new treatments must be better supported by early discussion between NHS England and companies to find solutions over funding," she said.

Evans noted it has been over a decade since the last dementia treatment was introduced in the UK, "People cannot afford further delays when the next breakthrough is made," she said. Alzheimer's Research UK also estimates that a new treatment able to delay the onset of dementia by five years could bring savings to the UK economy of £14.1bn a year – almost as much as the total NHS annual spend on medicines.

What about Wales and Scotland?

Wales has an NHS funding directive that requires the implementation of NICE's guidance. However, the Welsh NHS does not have to follow the new policies set out by NHS England and it is not bound by the £20m budget impact rule at the moment. "We will have to wait and see whether the devolved administration in Wales will follow a similar route as England," Williams said.

Scotland, which has its own HTA body, the Scottish Medicines Consortium, does look at NICE guidance for new medicines, but it only adopts these decisions if considered suitable. Its pricing body makes separate decisions based on its own appraisals.

Will there be further implications post-Brexit?

The new rules in England will fragment the UK healthcare system even more and serve to make the UK a less attractive market, Williams warned. "If there is going to be a substantial delay on access to new medicines then the UK is clearly not going to be the first to launch new medicines and clinical trials are not going to be carried out here because there is less benefit in UK clinicians gaining experience of new medicines," she said.

While Williams notes that Brexit has its own set of problems when it comes to drug research and market access, she said the new regulations on top of the UK leaving the EU will push the region further down the pecking order when it comes to accessing innovation.

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Will Physician Demand For Repatha Put Pressure On Payer Restrictions?

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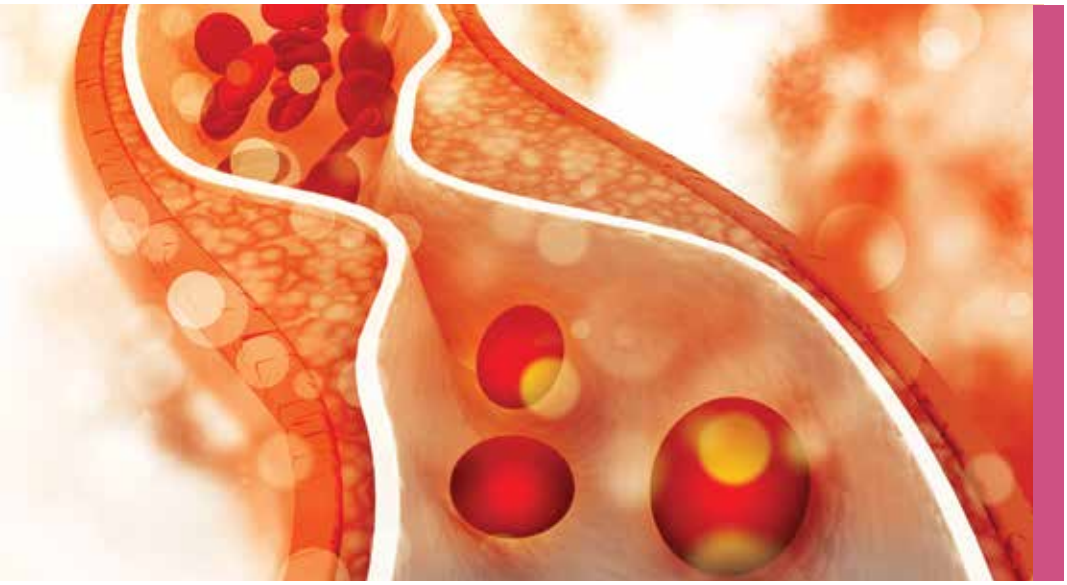

"Now that Repatha has proven a meaningful reduction in cardiovascular events, we expect payers to remove onerous barriers and help appropriate patients get access to Repatha," Amgen's Ofman said.

Physician demand could wind up being a determining factor in whether the reimbursement outlook for **Amgen Inc.**'s *Repatha* (evolocumab) improves following the long-awaited release of cardiovascular outcomes data for the PCSK9 inhibitor.

While the overall positive results of Amgen's FOURIER trial were announced last month, the level of benefit was unveiled March 17 at the American College of Cardiology annual meeting, in Washington, D.C. Repatha yielded a 15% reduction in a composite of major adverse cardiovascular events and no mortality benefit, short of expectations (*see box*).

But the benefit is being well received by practitioners and that might bring about enough increased demand to prompt payers to relax their utilization management criteria.

More important than how payers are responding to the data is "how physicians are going to respond to it," Real Endpoints CEO Roger Longman suggested in an interview. Payers do "nominally" cover Repatha and **Sanofi/Regeneron Pharmaceuticals Inc.**'s rival PCSK9 inhibitor *Praluent* (alirocumab) at the moment, albeit with "some challenging prior authorization requests," he noted.

"One of the big motivations for a payer to be a little more liberal in its interpretation of its own prior authorization criteria is the cost of saying 'no,'" Longman suggested. "From the payer point-of-view, the more it says no and the more times a physician appeals, the more the management cost is to the payer. If you have a lot of physicians prescribing and then appealing, that's a big cost. That could change coverage."

One study presented at ACC showed that 80% of Repatha and Praluent prescriptions are initially rejected, and more than half are never approved. Duke Clinical Research Institute's Ann Marie Navar, who presented the analysis based on prescription data from Symphony Health Solutions, reported patients may have to go through five appeals – and even once approved, one-third of prescriptions are not filled largely due to copay costs.

Express Scripts Holding Co. Chief Medical Officer Steve Miller told the *Pink Sheet* he did expect the FOURIER results to create more demand from physicians, at least for the labeled population. "Doctors will be a bit more enthusiastic, the question is will patients want to take an injectable drug," he said.

As to whether the level in benefit in FOURIER met expectations, Miller acknowledged that "there are probably mixed feelings in the market." However, he said, "the drug showed benefit in the right direction, maybe not the benefit some were hoping for, but it was incrementally better." Miller thought that the lack of a survival advantage was largely due to study design. "The question is whether is incremental enough to justify $14,000/year," the exec said.

Repatha's current wholesale acquisition cost is $14,523, though Amgen reports the net ranges between $7,700 and $11,200 per year.

This treatment category continues to be one where both payers and drug makers are experimenting with new payment approaches. Without going into details, Miller noted that Express Scripts is "actively" working on a new program with Amgen. The pharmacy benefit manager has been working on "several ideas" with both it and Sanofi, and will continue to do so.

AMGEN'S MONEY-BACK OFFER TO PAYERS

Amgen seems ready to preempt payer pushback by announcing new contracting options. "To underscore the company's conviction around these outcomes results, Amgen will offer additional contracting options in the US to payers willing to remove access barriers. These options include one that offers a refund of the cost of Repatha for all of their eligible patients who have a heart attack or stroke. In addition, Amgen will continue to offer innovative contracts that provide reasonable budget predictability to help address budget impact concerns raised by payers," the firm announced in conjunction with the FOURIER results.

The specifics will be negotiated with each payer, Amgen told the *Pink Sheet*, but "for any compliant Repatha patient who had a heart attack or stroke after taking Repatha for at least six months, payers would receive a refund in the form of an additional rebate."

"These robust data, from one of the largest outcomes trials ever conducted, validate that the net prices of Repatha in the market today are value-based. Now that Repatha has proven a meaningful reduction in cardiovascular events, we expect payers to remove onerous barriers and help appropriate patients get access to Repatha," Joshua Ofman, senior vice president of global value, access and policy, said in a statement. "We look forward to working with payers to improve the health of their patients at high risk of heart attacks and strokes and discussing innovative contracting options over the coming months." The company walked through how its price setting method reflects a value-oriented approach during an investor briefing from ACC. Amgen's material on the outcomes-

FOURIER Findings

- Double-blind, placebo-controlled trial in 27,546 patients with atherosclerotic CV disease and LDL levels of 70 mg/dL or higher while receiving statin therapy; patients were randomized to evolocumab 140 mg/2 weeks or 420 mg/month or placebo. Median duration of follow-up was 2.2 years.
- Median LDL was 92 mg/dL; 69% of patients were on high-intensity statins, 30% on moderate statins, 5% on ezetimibe. At 48 weeks, mean reduction in LDL of 59% for evolocumab compared to placebo, to 30 mg/dL. A quarter of the patients had LDL less than 20 mg/dL.
- For primary endpoint, evolocumab had a 9.8% rate of MACE vs. 11.3% for placebo (HR 0.85); on the key secondary endpoint evolocumab had a 5.9% rate of expanded MACE vs. 7.4% for placebo (HR 0.80)

Evolocumab reduced the risk of the primary endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization by 15%, and a 20% reduction on the harder secondary endpoint of CV death, MI or stroke. However, many analysts were expecting at least a 20% reduction on the primary endpoint and a mortality benefit – which was not demonstrated in the trial.

While there was no effect overall on cardiovascular death, lead investigator Marc Sabatine, Harvard Medical School, noted there were directional trends for death due to acute MI and death due to acute stroke. Evolocumab reduced the risk of MI or stroke by 21% to 27%. There was no difference for hospitalization for unstable angina.

"Over the past decade, none of the trials of intensive LDL lowering versus moderate statins showed a reduction in CV mortality," Sabatine pointed out, noting that with contemporary medicine, CV death "is less common than it was in the past." He similarly ascribed the lack of effect on unstable angina to the increased specificity of the assays used today, suggesting that probably most hospitalization for chest pain without biochemical evidence is likely not truly cardiac ischemia.

The study reinforces that long-term treatment matters, and longer follow up could reveal greater levels of benefit. "The magnitude of risk reduction with regard to the key secondary endpoint appeared to grow over time, from 16% during the first year to 25% beyond 12 months, which suggests that the translation of reductions in LDL cholesterol levels into cardiovascular clinical benefit requires time," Sabatine and co-authors say in the March 17 publication of FOURIER results in the New England Journal of Medicine.

Beyond the first year of treatment, evolocumab showed a 35% reduction in heart attack and a 24% reduction in stroke, Sabatine told Amgen's investor event.

Datamonitor Healthcare analyst Jack Allen commented that the risk reduction at five years, as has been shown in many statin trials, might show further benefit for evolocumab over placebo and should lower the number needed to treat to prevent an event.

The FOURIER results also confirmed Repatha's safety and the value of treating to low LDL levels, showing "continued cardiovascular benefit can be accrued even when LDL cholesterol levels are reduced to 20 to 25 [mg/dL], a range that is well below current targets," the article states.

The trial showed a clean safety picture across the board, including no signal in adverse events that had been areas of concern – like neurocognition and diabetes. There were no patients with neutralizing antibodies – which proved to be a major factor for Pfizer Inc.'s terminated PCSK9 inhibitor bococizumab.

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Amgen Says Repatha Outcomes Trial Backs Up Its Pricing Math
http://bit.ly/2nNgZtv

based contracts notes that contract options will be offered "to payers willing to remove access barriers."

In addition to a refund back to the payer for patients on Repatha who have a heart attack or stroke, "for what they spent on Repatha," Amgen is going to continue with other risk-sharing mechanisms that focus on LDL levels or cost predictability to the payer. Those include per-member/per-month contracts to help payers with cost predictability as volume changes over time and volume discounts.

Amgen already offered patient and provider support through its *RepathaReady* program, including copay assistance and insurance coverage support, as well as patient assistance for qualifying patients with no or limited coverage through the Amgen Safety Net Foundation.

The company thinks that the FOURIER data are enough to prompt payers to change their stringent usage criteria, which have held up utilization and sales of the drug. *(Also see "PCSK9 Inhibitors' First Birthday Brings Sluggish Sales And More Bad Press" - Scrip, 16 Aug, 2016.)*

WHAT'S THE PROBLEM?

It appears that access is not solely an issue of initial hurdles put up by payers. Other factors, such as adherence and the burden on patients' pocketbooks, also play important roles.

Both the sponsors and external sources have documented the difficulty in gaining coverage for PCSK9 inhibitors, which kept sales to $141m for Repatha in 2016. The Institute for Patient Access recently issued state-by-state health plan report cards showing rejection rates of about 50%.

Real Endpoints' Longman noted that many of the prior authorizations require patient adherence to both the PCSK9 inhibitor and the statin taken concurrently. At ACC, one poster estimated PCSK9 adherence at 59% and statin adherence can be even lower. "The PCSK9 problem is not simply a problem of PCSK9 coverage or adherence, it's a problem of statin adherence and therefore PCSK9 coverage," he said.

The Symphony Health Solutions data analysis presented March 19 by Duke's Navar showed that prescription volume has been increasing, but there has not been any improvement in payer approvals over time. The data captured 90% of retail pharmacies, 60% of mail-order and 70% of specialty pharmacies, on new prescriptions of Repatha and Praluent from Aug. 1, 2015-July 31, 2016.

Abandonment of prescriptions even after filled is high, at 34.7% of dispensed prescriptions (20.2% for commercial payers, 41.5% for Medicare). That rate was lower when a coupon program was used, Navar said, suggesting the copay is the major issue: abandoned prescriptions fell from 39.0% to 15.3% when a coupon was used.

Rejection rates are highly variable by PBM/payer, Navar reported, ranging from 33% to 75% for the top 10 PBMs by volume.

Navar acknowledged a limitation of the analysis was that it did not look at clinical factors, and that many of the rejections are "probably appropriately rejected." But, she added, "without change [in the rejection rates] over time, I do not think this is due to clinical factors alone."

"There's a disconnect between what providers are trying to do and what happens," Navar said.

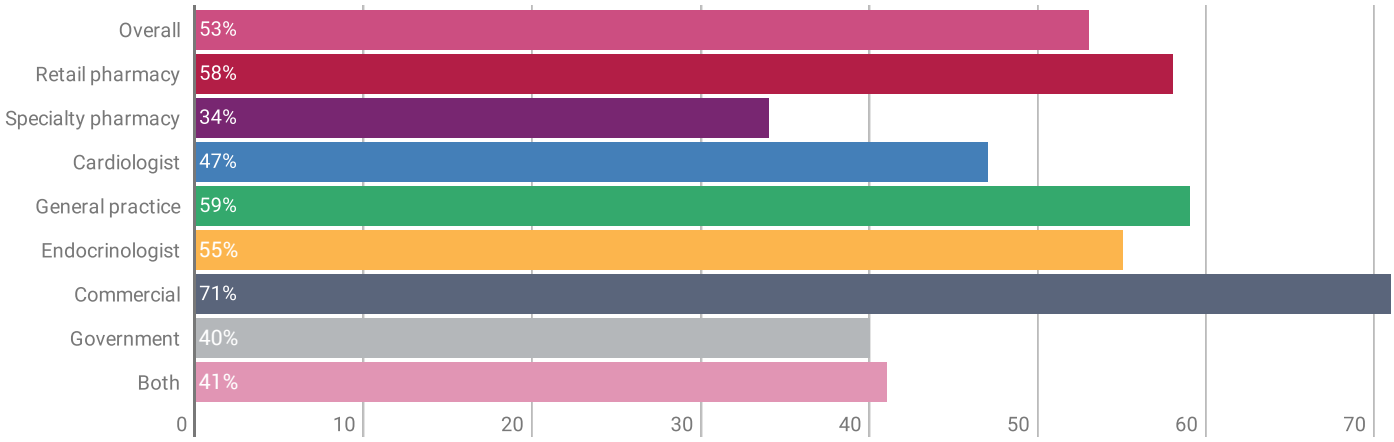
The researcher does expect trends will change now that outcomes data is available, certainly that demand for PCSK9 inhibitors will increase. "I suspect the prior authorization process currently is a very blunt instrument. Given the increased demand [from the FOURIER results] we need to look back at the prior authorization process and the burden on patients and the burden on providers," she said.

WHAT COULD CHANGE?

Amgen reports that payers are already changing utilization management criteria and that it has "numerous" risk-sharing contracts for Repatha in place.

But changes need to occur both with specific coverage requirements and with payers' overall perceptions of the PCSK9 inhibitors' value. Additional analysis of FOURIER will be necessary and payers and providers will look to changes in treatment guidelines.

PCSK9 Rx Rejection Rates



Source: A.M. Navar presentation at American College of Cardiology

In an interview at ACC, Cleveland Clinic cardiologist Steve Nissen said he expects the next iteration of treatment guidelines to endorse PCSK9 inhibitor use in high-risk patients and suggest it be considered in patients at moderate risk. Some expect the guidelines to change in the next year, though others expect the committee will wait for the publication of Sanofi's ODYSSEY OUTCOMES trial for Praluent in a peer-reviewed journal.

Greater changes in prescribing could come once subgroup analysis is done of FOURIER to clarify the risk reduction in the "ultra high risk patients" with comorbidities like diabetes or recent events. "These patients might get faster coverage, easier coverage, and the regular high risk patients might still be covered with these somewhat challenging restrictions," Longman predicted.

The number of patients that need to be treated to prevent an event is also a critical figure for payer calculations. In FOURIER, 74 patients needed to be treated for at least two years to prevent a cardiovascular (CV) death, heart attack or stroke. In another calculation in an appendix to the *New England Journal of Medicine* publication of the results, lead investigator Marc Sabatine, Harvard Medical School, noted that the number needed to treat to prevent one element of the composite endpoint over five years as used in a major meta-analysis of statin results (CTTC) was 17, "calculated by taking the annualized incident rate for the CTTC composite endpoint in the placebo arm (5.34%), multiplying that rate by 5, and applying the relative risk reduction (22%) in the CTTC endpoint after the first year (analogous to the CTTC approach to quantifying longterm benefit), which yields an absolute risk reduction of 5.9%, or a number needed to treat of 17."

"That's the kind of math that payers will need to be doing," Longman said. "Is the price of the drug, the offset here really worth it? It may be."

"A number needed to treat calculation is not a formal health economic assessment that can represent the value of a health care intervention in a holistic way," Amgen's Ofman stressed during the investor briefing. "It's almost never used," he added, by health authorities around the world. "It counts events only, not the impact of those events."

Published online March 19, 2017

FDA's NDA And BLA Approvals: Xadago, Bavencio, Symproic

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				
Pharmacare	Lamivudine/ zidovudine	Combination of the nucleoside analogue reverse transcriptase inhibitors (Combivir or for use with other antiretroviral agents for the treatment of HIV-1 infection	P, 4	3/17/2017
Newron	*Xadago* (safinamide)	MAO-B inhibitor indicated as adjunctive treatment to levodopa/ carbidopa in patients with Parkinson's disease experiencing "off" episodes *(Also see "Newron's Parkinson's Drug Xadago Has Narrower Indication Than Teva's Azilect" - Pink Sheet, 23 Mar, 2017.)*	S, 1	3/21/2017
Shionogi	*Symproic* (naldemedene)	Treatment of opioid-induced constipation in adult patients with chronic non-cancer pain	S, 1	3/23/2017
New Biologics				
EMD Serono	*Bavencio* (avelumab)	PD-L1 inhibitor blocking antibody for the treatment of adults and children 12 years and older with metastatic Merkel cell carcinoma		3/23/2017

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

Pharma Patents Are Vulnerable In Canada As Lilly Loses NAFTA Challenge

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Eli Lilly & Co. must fork over $5.2m after losing its unprecedented challenge of Canada's court system, but the entire industry will bear the brunt of the decision as pharma patents remain vulnerable to invalidity rulings.

Lilly claimed that the interpretation of patent law by Canadian courts violated the country's obligations to protect intellectual property under the North American Free Trade Agreement. Specifically, Lilly argued that the treaty obligates Canada to grant patents without discrimination as to field of technology and that Canada's new patent utility doctrine had impacted the pharmaceutical sector almost exclusively.

The company pursued arbitration against the government of Canada under NAFTA Chapter 11, which enables foreign investors to go before a tribunal to resolve disputes with treaty signatories. The International Centre for Settlement of Investment Disputes (ICSID) heard the case and issued a decision against Lilly on March 20.

At issue was the Canadian Patent Act's "promise utility" requirement that inventions be "capable of industrial application." The law requires that the promised utility be demonstrated or based on a "sound prediction" of utility at the time a patent application is filed and that it be disclosed in the original patent application.

In its 2013 arbitration complaint, Lilly said that since the advent of the doctrine in 2005 every patent invalidated for lack of utility involved a pharmaceutical patent. It sought CAD $500m (USD $375m) for revenue lost from the invalidation of its *Zyprexa* (olanzapine) and *Strattera* (atomoxetine) patents. *(Also see "O Canada! Lilly Claims Country's Invalidation Of Its Patents Violates NAFTA" - Pink Sheet, 19 Sep, 2013.)*

The ICSID panel of three arbitrators concluded that Lilly had "not demonstrated a fundamental or dramatic change in Canadian patent law," as required to succeed under NAFTA claims. And it found that Lilly had not proven that the promise utility doctrine discriminates against pharmaceutical patents.

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> "It would have been nice if the tribunal had said there is a point past which courts can't go in evolving patent doctrine"
> – UC Berkeley School of Law's Robert Merges

Lilly "argues that, in practice, the application of the promise utility doctrine has resulted in the invalidation of patents held by foreign firms only, and that the primary beneficiaries have been domestic generic drug manufacturers," the decision says. However, the only facts Lilly "has come close to establishing are that (i) since 1 January 2005, the pharmaceutical patents invalidated on the ground of inutility (whether through the application of the promise utility doctrine or not) have been held by foreign pharmaceutical companies, and (ii) the largest pharmaceutical companies in the world are not Canadian. The Tribunal will not infer discrimination from such a bare record."

25 DRUG PATENTS INVALIDATED

In a statement following the decision, the Pharmaceutical Research and Manufacturers of America said Canada has used the promise doctrine in 28 court decisions that invalidated 25 patents on 21 medicines over the last decade, targeting only pharmaceutical companies.

"We are disappointed that the tribunal's decision was made on narrow investment dispute grounds and did not even address whether Canada's 'promise' doctrine is consistent with NAFTA intellectual property rules," PhRMA said. "Canada remains the only country in the world that interprets patent utility in this manner, breaking the letter and spirit of its commitments on intellectual property rights."

PhRMA, the Mexican Association of the Research Based Pharmaceutical Industry (AMIIF) and the Biotechnology Innovation Organization had filed a motion to submit an amicus brief in support of Lilly but they did not submit a brief.

The Information Technology & Innovation Foundation also released a statement saying the tribunal's ruling is both faulty and contrary to actual evidence in failing to recognize the promise utility doctrine

represented a dramatic shift in policy.

A spokesperson for Global Affairs Canada said "the government of Canada welcomes the Tribunal's decision in this case."

University of California Berkeley School of Law professor Robert Merges, who was an expert witness for Lilly, said the statistics on patents found invalid under the promise doctrine are shocking. While fewer than 1% of US patents are invalidated for lack of utility, 40% of those under Canadian law are being invalidated for lack of utility.

The tribunal noted that in Merges' testimony he cited a survey of 239 cases in the United States over several years in which only one patent was found to be invalid for lack of utility.

Merges said national courts have a lot of leeway to bend and twist patent principles. "It would have been nice if the tribunal had said there is a point past which courts can't go in evolving patent doctrine," he said. "I'm afraid they'll [the ICSID tribunal] normalize pretty big swings in patent doctrine."

$14.6M LEGAL BATTLE

Lilly sought arbitration before the tribunal after an appellate court upheld trial court rulings invalidating its Zyprexa and Strateterra patents and the Canadian Supreme Court declined to intervene. In 2010, a federal court ruled in the Strateterra case that inventors claimed a new use for atomoxetine to treat attention deficit hyperactivity disorder and "implicit in this promise is that it will work in the longer term."

Regarding Zyprexa, Lilly's complaint noted that a federal court ruled in 2011 that the patent on the drug was invalid "because it failed to meet a construed promise of marked superiority over other known antipsychotic agents, which the court held implicitly included dosing over the 'long term.'"

In its statement of defense, the government of Canada said that Lilly had sought a second monopoly on olanzapine by claiming it had marked superiority in the treatment of schizophrenia compared with other compounds and the trial judge "reasonably and in accordance with Canadian law sought to determine whether, at the time of filing," Lilly had demonstrated that olanzapine had that utility or at least could "soundly predict that utility based upon its then-current research."

The government said Lilly's atomoxetine patent application asserting a new use for the compound "relied solely on a flawed and inconclusive preliminary study that it had failed to disclose in its application."

Lilly had sought damages of at least CAD $500m, which is roughly how much it believed it could have gained in the Canadian market if the patents were upheld through their normal life span. The Zyprexa patent was filed in Canada in April 1991 and would have expired in April 2011 and the Strattera patent was filed in Canada in January 1996 and would have expired in January 2016.

Now, as the losing party, Lilly must pay $4.4m to cover 75% of the Canadian government's costs as well as the $749,697 costs of the arbitration for a total of $5.2m. Lilly's own costs for the case were $9.4m, bringing the battle's tally to $14.6m.

The panel of arbiters gave Lilly a tip of the hat for the presentation of its case.

"Although Claimant has not succeeded in this arbitration, its claims were not in any sense frivolous and Claimant pursed them in good faith," they stated. "Indeed, it must be noted that both Parties displayed the highest level of professionalism, efficiency and courtesy in presenting their cases."

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MANUFACTURING QUALITY

Drug Compounder Acquitted Of Murder In Fungal Meningitis Outbreak Case

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A US jury has acquitted pharmacist Barry Cadden on all 25 counts of second degree murder for compounding purportedly sterile injectable drugs in a manner the government deemed recklessly out of compliance with US Pharmacopeia guidelines.

The federal jury nevertheless convicted Cadden of racketeering and 52 counts of mail fraud for shipping nonsterile drugs into interstate commerce. Sentencing is set for June 21.

The March 22 split verdict underscores the difficulty of obtaining a murder conviction even when there is egregious failure to assure the sterility of injectable drugs.

Cadden was owner and head pharmacist of the New England Compounding Center in Framingham, Mass., in 2012 when it shipped three lots of fungus-contaminated methylprednisolone

Contaminated vials like this one resulted in the largest public health crisis ever caused by a pharmaceutical product.

Photo credit: Justice Department trial exhibit

acetate (MPA) to health providers around the country.

The contaminated steroid, injected for pain relief, infected 753 patients' spinal fluids. Sixty-four died from fungal meningitis.

The crisis led Congress to pass legislation and FDA to shift its enforcement focus, if not to murder convictions.

A LONG-SIMMERING CONFLICT

The fungal meningitis outbreak came at a time when FDA had grown increasingly frustrated with its unclear authority over compounding of sterile injectables by state-regulated pharmacies. *(Also see "NECC Crisis Festered in Ambiguity That Reigns Over Compounding" - Pink Sheet, 29 Nov, 2012.)*

Photo credit: Justice Department trial exhibit

FDA investigators swab glovebox while inspecting NECC cleanroom during fungal meningitis outbreak.

There had been a steady stream of isolated contamination cases involving compounded sterile injectables over the years, but it was the NECC incident that triggered a massive response from the agency, with investigators inspecting compounding pharmacies all over the country in an effort to increase sterility assurance.

Legislation came along a year after the outbreak. The November 2013 Drug Quality and Security Act brought pharmacies that like NECC operated more like drug manufacturers clearly under the purview of federal drug GMP regulations.

The effort to convict Cadden and NECC clean room supervisor Glenn Chin of murder was based on a pattern of GMP violations deemed so egregious as to constitute "extreme indifference to human life." *(Also see "Murder in the Clean Room" - Pink Sheet, 30 Jan, 2015.)*

Chin's trial date is still to be determined.

DEFENSE: USP NO BASIS FOR MURDER CHARGES

Bruce Singal of the Boston law firm Donoghue, Barrett & Singal, who represented Cadden in the nine-week trial, told the Pink Sheet "one of the biggest lessons of this case is that the US Pharmacopeia standards and the company's own SOPs are a wholly inadequate foundation on which to base 25 charges of second degree murder."

Singal added that "I don't think the USP was designed as a standard for a criminal case, and particularly for murder. It's really best practices recommended by a private industry group."

The defense moved March 8 for acquittal by focusing on the difference between causation and regulatory noncompliance.

"From the very start, the government has pressed a faulty second degree murder theory that attempts to equate evidence of technical deficiencies at NECC with evidence of a malicious and depraved state of mind," the defense said.

This "litany of deficiencies" didn't show what caused the contamination, nor did it show any intent to commit murder, the defense argued.

The government did not prove Cadden had acted deliberately and recklessly "such that any reasonable person in his position would have known that death was highly and plainly a probably result from his actions."

Cadden didn't compound the contaminated methylprednisolone acetate himself; he didn't even work in the cleanroom, the defense argued. "At most, a manager's failure to take reasonable precautions to avoid deficiencies amounts to manslaughter, not second degree murder."

The motion went on to say that "the government's theory of how the MPA got contaminated is based entirely on testimony that NECC did not always clean or sterilize products in conformance with the recommended procedures under the USP. But the government has not shown that any of these deficiencies caused the contamination of MPA or any other drug."

ROLE OF EVIDENCE

Even though environmental monitoring showed mold and bacteria on floors "and less critical areas," Cadden's lawyers wrote, "the government has not presented any evidence – nor can it – that this mold or bacteria is linked in any way to the contamination of the MPA lots."

Furthermore, they asserted that the fungus responsible for the deaths, *Exserohilum rostratum*, was never identified at NECC.

They acknowledged the government's assertions of "lackadaisical cleaning," but argued there's no evidence showing that failure to clean in accordance with USP recommendations has anything to do with the contaminated lots.

Plus, there's no evidence that NECC's failure to autoclave product for the full 20 minutes that USP calls for "impacted the sterility of the autoclaved drug."

They went on to argue that even though NECC sent fewer samples to its testing lab than USP recommends, there is no amount of end-product testing that could confirm the status of the entire batch.

Moreover, the evidence "shows nothing but immediate and diligent efforts by Cadden and NECC to recall the drugs and alert all customers."

THE CASE AGAINST CADDEN

A March 12 filing against the acquittal motion provides a summary of the Justice Department's argument for the multi-state murder convictions.

The Justice Department said the evidence is clear "that Cadden operated the company in such an extraordinarily reckless manner, in total contravention of the standards set forth in USP 797, that it led to the largest public health crisis ever caused by a pharmaceutical drug."

Cadden directed NECC's high-risk sterile compounding operations and "had intimate knowledge and understanding of NECC's fraudulent compounding operations, and the danger those operations posed to patients," the government said.

For the previous three years, NECC had been autoclaving bulk MPA for 15 minutes instead of the 20 to 60 minutes that USP calls for, the government said. Furthermore, it took 11 minutes for the bulk product to heat up, so one expert said it was really only get-

ting four minutes of steam sterilization.

An FDA microbiologist found two types of fungi in a container of autoclaved MPA that FDA had seized during execution of a search warrant.

The plaintiffs said Cadden knew NECC wasn't testing MPA and other products properly for sterility, and was shipping product before receiving sterility test results.

They cited one case where lab results came back positive for contamination of a lot NECC had already shipped to a hospital. Cadden instructed his quality control officer to just tell the lab the lot was discarded.

Further, NECC was testing bulk solution rather than vials, and so failed to account for contamination that may have occurred during vial filling.

NECC was testing only one vial per batch rather than as many as 20 vials to meet USP guidelines.

'BOTCHING LOTS'

The pharmacy also would, at Cadden's direction, put lot numbers from tested lots on vials filled with drugs from untested lots, a practice called "botching lots."

In one August 2011 email, Cadden instructed cleanroom supervisor Glenn Chin to "make as many lots as you like 'internally' but only label vials with lot # of tested lots to cover our ass."

Cleaning and environmental monitoring was subpar, Justice said, noting that one employee told the jury some monthly cleanings were missed to give more time for production.

The QC officer testified that in 2012, "there was a lot of mold." When it was particularly bad, she would show Cadden the petri dishes, which were covered with it. And even then, the government said she told the jury "no microbiologist was ever consulted, no extra cleaning was ever performed and drug production never stopped."

The government argued that the evidence it had presented "reveals that Cadden's actions fell far below the standards set forth in USP 797 as it relates to sterilization of drugs, and cleaning and environmental monitoring of the clean room."

From the editors of the Gold Sheet. Published online March 22, 2017

Need For Consensus On Pharmacovigilance For Drugs In Pregnancy Delays New EMA Guideline

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The European Medicines Agency's new guideline on optimizing pharmacovigilance practice for medicines taken during pregnancy and breastfeeding has been delayed to take into account the need for building consensus with all stakeholders and will now be issued for public consultation towards the end of this year.

The EMA's pharmacovigilance risk assessment committee (PRAC) was initially due to be consulted on the draft version of the guideline in the second quarter of 2016. This will now take place in Q2/Q3 this year, with PRAC aiming to adopt the draft guideline in Q3/Q4 2017.

The initial timeline proposed to develop the guideline was "adjusted to take into account the need for consensus building," an EMA spokesperson told the *Pink Sheet*. When ready, the document will include pharmacovigilance and risk minimization activities in relation to:

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- medicines taken during pregnancy
- medicines taken during breastfeeding
- longer term effects of medicines taken before and during pregnancy and breastfeeding on infants, children and adolescents.

The guidance document will be included as a new chapter (P III) under the EMA's good pharmacovigilance practice (GVP) guideline on product- or patient-specific considerations.

The EMA is also developing a new chapter (P IV) on pharmacovigilance requirements for geriatric population. It intends to publish the geriatrics guideline for public consultation in the third quarter of 2017. The aim of this guidance will be to take into account specific issues such as altered physiology, frailty and frequent comorbidity in pharmacovigilance processes, the agency spokesperson said.

The EMA has already issued two other chapters on product- or patient-specific considerations under its GVP guideline on: vaccines for prophylaxis against infectious diseases (P I); and biological medicinal products (P II). *(Also see "EU Regulators Ramp Up Safety Monitoring Efforts For Biologicals" - Pink Sheet, 5 Feb, 2016.)*

From the editors of Scrip Regulatory Affairs. Published online March 22, 2017

Will Primatene Mist Inventory Ever Leave The Warehouse?

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> "We do believe there may be some misunderstanding with some of the data that we've submitted" on the Primatene Mist application – Amphastar President Jason Shandell

Amphastar Pharmaceuticals Inc.had manufactured around $500,000 of its *Primatene Mist* OTC emergency asthma inhalers for a planned relaunch, now stymied by FDA's delay of an approval decision. The agency's request is "frustrating" the firm and puzzling analysts.

A meeting with FDA to discuss the action is expected during the second quarter of this year. The company also hopes to meet with the agency to discuss its intranasal naloxone opioid overdose treatment which similarly received a complete response letter and request for information.

The Primatene Mist NDA would return the actuated epinephrine inhalation aerosol inhaler to the market with the same epinephrine formulation used in the original product but using a different propellant, with hydrofluoroalkane replacing ozone-depleting chlorofluorocarbons.

During the Rancho Cucamonga, Calif., firm's 2016 fourth-quarter and full-year earnings briefing on March 13, President Jason Shandell said upon receiving FDA's second complete response letter for the NDA in December, "it was frustrating to hear that they think an additional study is needed."

The December CRL, about two years after the first one, requested additional changes to the labeling and packaging for the product in addition to another human factor validation study to assess consumers' ability to use it without the guidance of a doctor or pharmacist. *(Also see "Primatene Mist CRL Underscores Challenges For OTC Asthma Treatments" - Pink Sheet, 4 Jan, 2017.)*

"They think that some further improvements to the label could be made to even further increase the ability of potential consumers to understand this," said Shandell in response to analysts' questions about the chances of the Primatene Mist NDA.

CONCERN ABOUT OTC ASTHMA PRODUCT

FDA's concerns are not about epinephrine's safety and efficacy and the reliability of the replacement propellant. Rather, in addition to questions on labels effectively guiding correct use of the inhaler, the agency has heard from advisory committees and other health care experts stating concern about whether consumers would

SALES OFF 17%

Amphastar reported a net loss of $2.7m, 6 cents per share, for the fourth quarter after showing net income of $7.5m, 16 cents per share, in the prior-year period.

Sales for the October-December period fell 17% to $63.5m. The brunt of the decrease came in a 58.3% plummet in sales of enoxaparin, used as an anticoagulant and for deep vein thrombosis, to $8.3m due to the end of a distribution agreement with **Actavis** that delayed shipping units for the retail market from August until the end of December, and a 56.1% fall to $4.7m in insulin API sales as it restructured an agreement that delayed **MannKind Corp.**'s purchase obligations.

The firm said other finished pharmaceutical product revenues grew 10% to $50.6m on increased sales of epinephrine, which offset pricing-related declines in its naloxone business.

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use Primatene Mist only as an emergency treatment or rely it on it inappropriately as their ongoing asthma remedy. *(Also see "FDA Panel Votes Against Primatene Reboot Due To Safety Concerns" - Pink Sheet, 26 Feb, 2014.)*

For Amphastar's part, the firm has provided research data FDA has requested and is not aware of what additional information would be needed to support safe and effective nonprescription use of Primatene Mist.

Shandell said before conducting another study and submitting additional data that also might prompt a CRL, Amphastar will meet with agency officials just to learn its next step, and potentially to clarify that it already has provided all data needed for approval of the NDA.

"We do believe there may be some misunderstanding with some of the data that we've submitted, and that's the reason why we're seeking meetings with the agency for clarification," Shandell said.

During the briefing, Jefferies analyst David Steinberg called FDA's response so far to the Primatene Mist NDA "a bit of a head-scratcher" and suggested that the agency might be hesitant to approve an OTC emergency asthma inhaler.

PRIMATENE STILL AN ASSET

In a Jan. 16 research note following a meeting with Amphastar executives, Steinberg and Jefferies colleague Edward Chung said they are keeping Primatene Mist with peak annual sales of around $80m in their calculations for the firm's performance and anticipate a 2018 second-half launch.

Still, they "got the sense" the firm "was very surprised to receive a second Primatene CRL given their regular communication with the FDA throughout the regulatory process," according to their report.

Steinberg and Chung also noted that FDA advisory committees have voted against approving the Primatene Mist NDA and again allowing OTC sales of an emergency asthma treatment.

"We admit there is a possibility that Primatene HFA never makes it to market as an OTC product given the protracted development period and the negative 2014 FDA Advisory Panel vote," they wrote.

However, they said they "continue to expect ultimate approval" largely because the original Primatene Mist was available OTC for more than 50 years before FDA ordered Amphastar to pull the product to comply with an international treaty banning chlorofluorocarbons use.

The agency initially imposed a 2008 deadline on ceasing distribution of Primatene Mist but allowed two extensions and the product was available from the firm through 2011. *(Also see "Armstrong Juggles Reformulating Primatene Mist, Pushing To Sell Existing Inventory" - Pink Sheet, 23 Jul, 2012.)*

Amphastar also reported its fourth-quarter research and development costs increased 40% to $12.3m. Chief Financial Officer Bill Peters said the increase partly came from a $1.1m inventory expense related to Primatene Mist, with about half for components and the other half "was finished goods that we had manufactured."

Should the firm gain approval to market Primatene Mist, the existing finished products could be distributed, helping Amphastar relaunch the product "at a very discounted inventory number," Peters said.

He said the firm has increased spending on its pipeline products, both in APIs and components including "somewhat expensive" inhalation items. "As we move forward, we are expensing both the API and the cost of the devices," Peters said.

> "Jefferies analysts said Amphastar's statement on FDA's requests adds some uncertainty to the naloxone application.

LONGER DELAY FOR NALOXONE?

Human factors also figured into the complete response letter for intranasal naloxone. Shandell said FDA identified four "primary issues" about the opioid receptor agonist: improving its human factors validation study; modifying the product's delivery accuracy verification method; improving the standards for its reliability; and adjusting the volume per actuation to account for pediatric use, including neonates.

In a research note following the earnings briefing, the Jefferies analysts said Amphastar's statement on FDA's requests adds some uncertainty to the naloxone application. "Given these technical challenges we believe there could be a more protracted delay with this program," they said.

Amphastar is among the firms marketing naloxone generics for injection, but demand for immediate action when an overdose is suspected has spurred development of formulations more easily administered by non-professionals. The human factors study would involve whether users can understand instructions provided for novel naloxone products approved for community use and can perform critical tasks. *(Also see "Amphastar's Naloxone Nasal Spray Delayed; User Human Factors Study Among FDA Concerns" - Pink Sheet, 21 Feb, 2017.)* An FDA advisory committee reviewing the application also raised questions about whether the efficacy standard should be revised for these products in light of use of increasingly powerful synthetic opioids. *(Also see "Higher Naloxone Doses Narrowly Favored By FDA Panel" - Pink Sheet, 5 Oct, 2016.)*

FDA has approved two community-use naloxone products: the auto-injector *Evzio*, approved in 2014 but recently relaunched by **kaleo Inc.** after **Sanofi** dropped it, and **Adapt Pharma Ltd.**'s nasal spray, approved in 2015 under the *Narcan* brand. *(Also see "Amphastar's Naloxone Nasal Spray Delayed; User Human Factors Study Among FDA Concerns" - Pink Sheet, 21 Feb, 2017.)*

The Adapt product not faced direct competition as other potential competitors as well as Amphastar have received CRLs. FDA requested more clinical pharmacology data for **Indivior PLC** and AntiOp's naloxone nasal spray NDA in 2015.

From the editors of the Tan Sheet. Published online March 20, 2017

OTC Allergy Drug Use Increases: A Symptom With Multiple Causes

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US OTC switches of three intranasal corticosteroids and an oral antihistamine ingredient since 2007 are pushing an increase in consumer use of nonprescription allergy treatments and a decrease in Rx drug use, says the Consumer Healthcare Products Association.

While the industry trade group says growing use of allergy OTCs from 2009 through 2015 is a sign of more consumers prioritizing self-care over using health care services, allergy specialists said in interviews that their patients often have to start treatment with an OTC. That's because with most allergy ingredients available OTC, insurers often require patients to try a nonprescription version of an ingredient before an Rx product is covered.

"I don't have any patients who could walk into a pharmacy right now and have their insurance cover paying for an allergy drug prescription without trying an OTC drug first," said Rajan Merchant, an allergy, asthma and immunology specialist with Dignity Health in in Sacramento, Calif.

On the other hand, consumers relying on an OTC product before consulting a doctor could be wrong about their allergy type and could choose the wrong ingredient for their symptoms, say Merchant and Julie McNairn, another specialist suggested by the American Academy of Allergy, Asthma & Immunology to offer insight on allergy treatments.

"I don't think most consumers realize what the ingredients are," said McNairn, an allergist and immunologist with Allergy and Asthma Associates in Ithaca, N.Y.

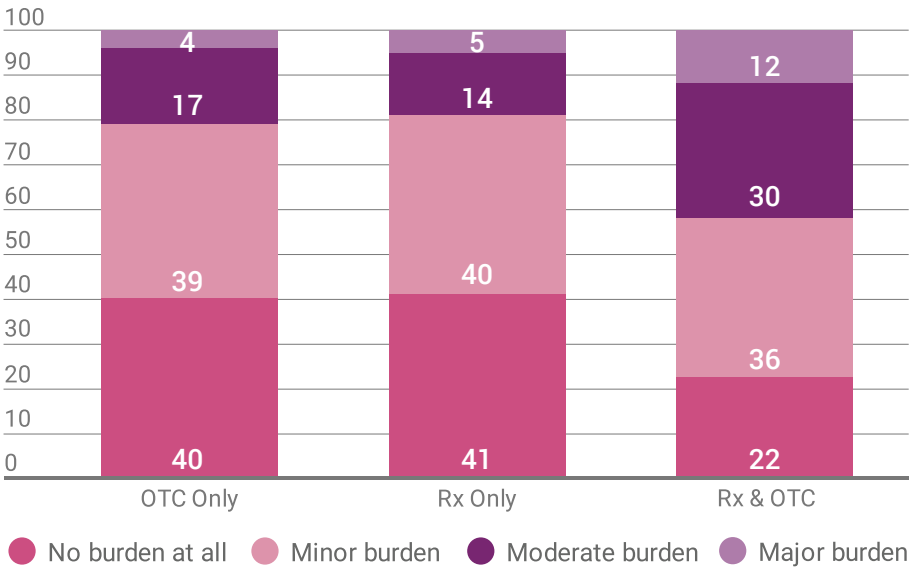
According to results of a July 2016 survey CHPA commissioned, the percentage of allergy sufferers using only OTC drug remedies for allergies has increased from 53% in 2009 to 60% in 2015. At the same time, the percentage who receive a health care provider's treatment for allergies decreased from 31% in 2009 to 28% in 2015, Nielsen Homescan data included in the survey show.

ANALYZE

Visit our website for an interactive chart on: **Consumers' Allergy Rates And How They Respond**
http://bit.ly/2nQpynK

"The implication here is that allergy sufferers in some cases are increasingly self-treating their symptoms," CHPA says in its report on the survey, which also included information from IMS Health on consumers' spending on Rx drugs and health care services and from questions asked of 2,000 consumers.

'Burden' Similar Across Remedy Types



Consumers reporting using only OTC or only Rx drugs to treat their allergies also reported similar financial burden levels.

Source: CHPA and Nielsen Homescan survey

TARGET MARKET GROWS, TOO

The survey also shows that the number of consumers who say they have allergies has edged up, from 26.9% in 2009 to 27.8% in 2015. CHPA says that taking into account population growth and the survey results, it projects 9.7m more consumers had allergies in 2015 than had them five years earlier.

With more consumers reporting they have allergies, the number using OTC remedies will correspondingly increase.

The survey also stated, Merchant pointed out, that almost half of the respondents said they asked a doctor and 23% said they asked a pharmacist to recommend an OTC allergy drug.

"More than half the patients still are asking for advice," said Merchant, who also is a clinician and a clinical researcher Woodland Medical Group.

And when physicians determine that a patient needs a treatment for allergies, their first step is prescribing the appropriate Rx ingredient, he added. "We haven't changed our treatment guidelines."

McNairn observed that unless their patients inform them, physicians don't know how they react to OTC allergy drugs, which, although safe, still could cause potentially harmful side effects, or whether a certain ingredient is effective.

"That's the disservice that's going on here," she said.

Although nonprescription allergy drugs have histories of safe use, one criteria for a drug to be available OTC is an indication for a self-limiting condition, Merchant said. "Allergies are not necessarily considered self-limiting," he said.

The first intranasal corticosteroid approved as an OTC, **Sanofi**'s *Nasacort Allergy 24HR*, prompted concerns about growth suppression in children and inadequate long-term use data to garner a positive recommendation from FDA's Nonprescription Drugs Advisory Committee in 2013. *(Also see "Nasacort AQ Switch Gets NDAC Nod Despite Pediatric Use Concerns" - Pink Sheet, 5 Aug, 2013.)*

An American Academy of Allergy, Asthma & Immunology task force in 2006 advocated against switching intranasal corticosteroids due to their potential for overuse, complications from adverse effects and serious associated risks including bone resorption – by which bones begin to lose substance – as well as growth suppression and ocular effects such as glaucoma and cataracts. *(Also see "Steroid Nasal Sprays Not Suitable For Rx-to-OTC Switch – Task Force" - Pink Sheet, 22 May, 2006.)*

COSTS INFLUENCE SATISFACTION

From its questions for consumers, the survey showed that among those who only take OTCs to treat allergies, 87% said they are satisfied, the highest satisfaction rate among groups that respond differently to the conditions. Respondents who take both an Rx and OTC concurrently to treat allergies expressed the lowest satisfaction with their medication options, 81%.

"This could be likely due to the level of severity of their allergies, or possibly the costs associated with managing their symptoms," CHPA suggests.

As consumers have fewer doctor visits, they also are lowering their overall spending on allergy treatments. Consumers treating with OTCs only discuss their allergies with their doctor or other health care professional an average of 1.5 times per year, spending about $37.56 in co-pays for allergy-related health care services.

Consumers opting for Rx-only allergy treatment see a doctor for the condition an average of 2.2 times per year, spending $55.09 in co-pays, and those using both Rx and OTC drugs seeks health care an average of 6 per year, accounting for $150.24 in co-pays.

Costs likely are the key influence on consumers using OTC allergy drugs without also seeking a doctor's diagnosis, McNairn observed.

"It's ultimately a cost issue and an access issue," she said. "The insurance programs are covering fewer and fewer prescription allergy drugs."

DUAL USAGE STEADY

The survey showed that of consumers with allergies, more than 90% of take some type of medication to manage their symptoms. CHPA says consumers have adjusted their behaviors as more OTC allergy drugs are available, with 66% in 2009 and 75% in 2015 purchasing an OTC either on its own or in conjunction with an Rx product.

However, with more consumers opting for OTC-only treatment, as the overall number using some type of allergy product increased, the percentage who take both an Rx and an OTC medication stayed relatively flat, 13% to 15%, over the five-year period analyzed.

The data also showed consumers' level of engagement with OTCs depends on the severity of symptoms. Households most engaged with the OTC products report moderate allergies, while the least engaged with the products have severe allergies, implying that the more severe an allergy, the more likely a prescription drug will be needed.

The survey's Nielsen Homescan component also found changes in spending on allergy OTCs, from around $33 for an average household on 2.9 trips to retail outlets in 2009 to $39 on the same number of trips in 2016.

From the editors of the Tan Sheet.
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3 CORTICOSTEROIDS, 1 ANTIHISTAMINE

The four ingredients with allergy indications moved from Rx to OTC in the US and noted in the survey report comprise three intranasal corticosteroids, each a consumer products sales driver for its marketer, and an oral antihistamine that also is a key consumer brand for its marketer.

The antihistamine is cetirizine, approved for OTC in 2007 through **Johnson & Johnson**'s switch application for its *Zyrtec* product and launched 2008, though private label versions from **Perrigo Co. PLC** reached store shelves before the brand. *(Also see "Zyrtec Launch Brings Big Boost To Johnson & Johnson, But Competition Grows" - Pink Sheet, 21 Apr, 2008.)*

The first intranasal corticosteroid ingredient available OTC was approved in 2013 through **Sanofi**'s proposal for triamcinolone acetonide, which it markets nonprescription as *Nasacortrx Allergy 24HR*. *(Also see "Sanofi's Nasacort First-In-Class Switch Receives FDA Approval" - Pink Sheet, 11 Oct, 2013.)*

GlaxoSmithKline PLC was second to the OTC intranasal corticosteroid market with fluticasone propionate, available in its *Flonase Allergy Relief* product approved in 2014. *(Also see "Flonase Allergy Relief Exclusivity Sliced Up By Label Carve-Out" - Pink Sheet, 10 Feb, 2015.)*

Under license from **AstraZeneca PLC**,J&J markets the third ingredient in the category, budesonide, available in *Rhinocort Allergy 24HR* since approval in 2015. *(Also see "Rhinocort Switch Makes Three In OTC Intranasal Corticosteroid Market" - Pink Sheet, 26 Mar, 2015.)*

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Genentech's rituximab/hyaluronidase injection for treatment of patients with: relapsed or refractory follicular lymphoma as a single agent; previously untreated follicular lymphoma in combination with first-line chemotherapy and, in patients achieving a complete or partial response to rituximab/hyaluronidase in combination with chemotherapy, as single-agent maintenance therapy; non-progressing (including stable disease) follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine and prednisone chemotherapy; previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone or other anthracycline-based chemotherapy regimens; and in combination with fludarabine and cyclophosphamide for previously untreated and previously treated chronic lymphocytic leukemia	Oncologic Drugs	March 29
Array BioPharma's binimetinib for treatment of patients with unresectable or metastatic melanoma, with NRAS Q61 mutation as detected by an FDA-approved test, who have received prior treatment with checkpoint inhibitor therapy	Oncologic Drugs	March 29
Safety issues associated with over-the-counter analgesic combination products used for upset stomach (i.e., heartburn, nausea, fullness, belching, gas, acid indigestion, and/or sour stomach) and hangover indications under the Internal Analgesic and Antacid monographs; discussion of the hangover indication under the Overindulgence, Internal Analgesic and Stimulant monographs	Nonprescription Drugs; Drug Safety and Risk Management	April 4
Novo Nordisk's nonacog beta pegol (recombinant human coagulation Factor IX, glycopegylated) for hemophilia B	Blood Products	April 4
Inspirion Delivery Sciences' oxycodone immediate-release for management of moderate-to-severe pain where the use of an opioid analgesic is appropriate; committees will discuss the overall risk-benefit profile and whether applicant has demonstrated abuse-deterrent properties that would support labeling	Anesthetic and Analgesic Drug Products; Drug Safety and Risk Management	April 5

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