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# TOO BOLD BY HALF: Allergan's Latest Moves And Pharma's Leadership Deficit

MICHAEL MCCAUGHAN pinkeditor@informa.com

A year ago, **Allergan PLC** staked out an unlikely position as a leader in corporate responsibility, announcing a "social contract" that included the first formal pledge by a leading biopharma company to restrain price increases in response to headlines and hearings criticizing "outrageous" pricing for older brands.

At the same time, Allergan embraces a new identity as a "bold" company, changing its boilerplate language in press releases to say: "Allergan plc, headquartered in Dublin, Ireland, is a bold, global pharmaceutical company and a leader in a new industry model – Growth Pharma."

"Bold" replaced "unique" in that sentence.

The idea of Allergan claiming the role as industry leader in responsible pricing in the US was itself bold. As the Allergan tagline makes clear, the company may have roots in New York City (Forest) and California (Allergan), but it is based in Dublin to limit its tax exposure. And the aggressive marketing heritage of the two predecessor companies certainly didn't fit well with industry's usual approach of emphasizing research and development as the core of its image, at least in political contexts. Allergan has since been joined by a handful of Big Pharma companies in some form of pricing pledge, but – particularly among the large US companies– no one has stepped forward in anything like the "bold" way Allergan did. For better or for worse, Allergan still stands out as defining the industry's view of social responsibility.

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The company's latest "bold" move should remind the rest of the industry how dangerous that is.

In a headline that could almost read like a joke, Allergan has transferred its patents for the blockbuster dry eye therapy Restasis to the Saint Regis Mohawk Tribe. The intent: to take advantage of the tribe's status as a "sovereign nation" to pre-empt efforts to invalidate the Restasis patents via the inter partes review (IPR) process. *(Also see "Allergan Shifts Restasis Patents To Native American Tribe To Invoke Immunity From IPR" - Pink Sheet, 9 Sep, 2017.)*

To be clear, there is nothing wrong with a company using every legal means to defend its intellectual property. Being creative and aggressive can be tremendous virtues, and this strategy could well pay off dramatically for Allergan's investors. Just don't confuse that with social responsibility.

To his credit, Allergan CEO Brent Saunders isn't ducking the issue. In an interview with the Pink Sheet (and, in understandably briefer form, in an exchange on Twitter) Saunders emphasized that Allergan's social contract includes investing in innovation, and those investments are possible only with protections for intellectual property.

Saunders stressed that Allergan is fully prepared to adjudicate the validity of its patents via the 35-year-old Hatch/Waxman process – but the company views the separate IPR process as a form of double jeopardy. Saunders isn't alone in that view: it is something like the consensus of the innovator biopharma sector that the IPR process is something of an abomination.

CONTINUED ON PAGE 4


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'Believe it or not, we don't have as many disease-specific guidances as you would suspect on the new drug side,' Commissioner Gottlieb says.

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US advisory committee unanimously impressed by the 90% plus efficacy; FDA says label may note lack of data in those who've previously had shingles.

**Australia's Provisional Approval Pathway Prompts Industry Concerns Over Data Provision**

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Pharmaceutical industry responses to a consultation by Australia's Therapeutic Goods Administration on a provisional approval pathway have revealed concerns over whether companies will be able to provide adequate data. Companies have also advised the TGA to look to other regulators, including the European Medicines Agency, for inspiration.

**Making Imodium Rx-Only No Help On Curbing Opioid Abuse – CHPA**

https://pink.pharmamedtechbi.com/PS121528

Making OTC diarrhea remedy loperamide Rx-only is unlikely to reduce abuse and would cause problems for millions of US consumers who depend on the product, says the Consumer Healthcare Products Association, responding to a petition advocating the change.

**Jazz On Track With Q4 EU Filing for Leukemia Treatment Vyxeos**

https://pink.pharmamedtechbi.com/PS121542s

As European regulators this week consider whether to fast-track the eventual regulatory review of Jazz Pharmaceuticals' treatment for acute myeloid leukemia, the company says it is on track to file for EU regulatory approval this year.

# inside:

CONTINUED FROM COVER

## RESTASIS' LONG PATENT LIFE

But let's just say it's a stretch to paint Allergan as a victim of an injustice of US IP law.

To start with: Restasis was approved by FDA in December 2002. That means that Allergan has already benefited from 15 years of effective patent life for the product. Allergan, however, says its patents on the product run until 2024 – or 22 years after FDA approval.

That's a pretty long run for a pharmaceutical patent. But it is an especially long run for patent on a new formulation – which is what Restasis is.

The active ingredient is cyclosporine – truly a revolutionary medicine when it was first launched in 1983 for use in organ transplant patients to prevent rejection. The drug was developed by **Sandoz Inc.** (now pat of **Novartis AG**), and went generic in 1998 – 15 years after FDA approval. It seems hard for Allergan to claim that it would be unjust if it faces generic competition for an ophthalmic formulation after the same period of exclusivity.

Now, patents are patents and if they are valid Allergan is entitled to enforce them. But, if the patents are valid, there is no reason to think the IPR process would invalidate them. The IPR process may or may not be a good idea – but it is part and parcel of the same system that granted Allergan the patents in the first place.

Allergan thus appears to be trying to avail itself of the aspects of US intellectual property law that it likes (including, incidentally, the unique pricing climate for innovator drugs), while evading aspects of the law it doesn't like.

That may be creative and bold – but it is hard to defend politically.

It doesn't help that the strategy echoes other tactics that industry's critics hold against it. First, the fact that the strategy to negate the IPR involves the transfer to a "sovereign nation" begs to be compared to the "inversion" strategy behind international mergers to escape US taxes. Then there is the fact that Allergan is transferring IP to the Mohawk tribe – and paying the Mohawk tribe to take it. If that doesn't beg to be compared to "reverse payment" patent settlements, what does?

"Allergan appears to be trying to avail itself of the aspects of US intellectual property law that it likes (including, incidentally, the unique pricing climate for innovator drugs), while evading aspects it doesn't."

All of which would be bad enough if Allergan weren't the self-appointed champion of corporate responsibility for biopharma companies. But Allergan has "boldly" seized that mantle.

## ALLERGAN VS. IMPRIMIS

If the danger isn't clear enough, consider this coda. On Sept. 7, the day before the Restasis deal was announced, Allergan took another "bold" action – filing a lawsuit against the pharmacy compounder **Imprimis Pharmaceuticals Inc.** and several other firms, claiming they are illegally marketing unapproved drugs (including versions of Allergan products).

Imprimis, in some cases at least, does so proudly: at the height of the controversy over Turing's *Daraprim,* the company publicly announced availability of a compounded alternative for $1 a dose. *(Also see "Express Scripts Turns To Compounding To Fight High-Priced Off-Patent Drugs" - Pink Sheet, 1 Dec, 2015.)*

In its fight against Allergan, however, Imprimis isn't about to cede the high ground. Here is how the company describes Allergan in its own press release responding to the suit:

"Allergan is a well-known professional litigant. Here are some of Allergan's recent run-ins with the law:

- In order to avoid paying US taxes, Allergan, which was a California-based US corporation, abandoned the United States in a legal maneuver called a tax inversion.
- Allergan has been the subject of Federal Trade Commission crackdowns for paying generics companies to delay selling lower cost products.
- In the heat of Congressional hearings on drug price gouging by Big Pharma, Allergan promised to 'only' raise its already high drug prices less than 10% per year. US inflation rates have averaged 1.1% over the past four years.
- Allergan division executives have been arrested and subjected to US Justice Department criminal action for allegedly employing illegal sales tactics.
- Allergan has paid off millions of dollars in whistleblower lawsuits by its own former employees, alleging myriad nefarious Allergan business practices.
- Allergan is currently being sued by numerous states' Attorney's General for allegations related to illegal 'marketing schemes' connected to its opioid products.
- Allergan pled guilty to 'misbranding' and 'off-label promotion' of its flagship Botox product, and was forced to pay over one-half billion dollars in fines to the federal government.
- Despite FDA warnings that Allergan's Viberzi product 'could result in hospitalization or death' for vulnerable patient populations, Allergan continues to advertise it widely.
- To thwart the US legal system and avoid lower-cost generic competition, Allergan has schemed to sell patents for its Restasis drug to a Native American tribe."

To be clear, Allergan is much more than a "professional litigant." But its record of "bold" actions – including its latest patent defense strategy – should make clear that it is not the best company to have out in front as an image of Big Pharma "responsibility" in a charged political climate.

*From the editors of the RPM Report.*
*Published online September 12, 2017*

# NDA User Fees Will Climb Almost 16% On Oct. 1

**DERRICK GINGERY** derrick.gingery@informa.com

With less than three weeks to go before the launch of the new user fee cycle, the US FDA has officially announced the rates that sponsors of biosimilars and novel drugs will have to pay.

In announcements scheduled to be published in the Federal Register on Sept. 14, the agency set the rates for biosimilar and prescription drug applications in Fiscal Year 2018, which begins Oct. 1. The fee changes are detailed in the following table, which also include the generic user fees announced last month.

*Published online September 13, 2017*

## Prescription Drug User Fees

| TYPE | FY 2017 | FY 2018 | CHANGE |
|---|---|---|---|
| Application requiring clinical data | $2,038,100 | $2,421,495 | $383,395 (15.8%) |
| Application not requiring clinical data or supplement requiring clinical data | $1,019,050 | $1,210,748 | $191,698 (18.8%) |
| Establishment* | $512,200 | N/A | N/A |
| Product* | $97,750 | N/A | N/A |
| Program* | N/A | $304,162 | N/A |

## Generic Drug User Fees

| LEGACY GDUFA FEES | FY 2017 | FY 2018 | CHANGE |
|---|---|---|---|
| ANDA | $70,480 | $171,823 | $101,343 (144%) |
| Prior Approval Supplement** | $35,240 | $0 | $35,240 (-100%) |
| Drug Master File | $51,140 | $47,829 | -$3,311 (-6.5%) |
| Domestic Active Pharmaceutical Ingredient Facility | $44,234 | $45,367 | $1,133 (2.6%) |
| Foreign Active Pharmaceutical Ingredient Facility | $59,234 | $60,367 | $1,133 (1.9%) |
| Domestic Finished Dosage Form Facility | $258,646 | $211,087 | -$47,559 (-18.4%) |
| Foreign Finished Dosage Form Facility | $273,646 | $226,087 | -$47,559 (-17.4%) |

| NEW GDUFA II FEES | AMOUNT |
|---|---|
| Domestic Contract Manufacturing Organization | $70,362 |
| Foreign Contract Manufacturing Organization | $85,362 |
| Program Fee-Large size operation generic drug applicant | $1,590,792 |
| Program Fee-Medium size operation generic drug applicant | $636,317 |
| Program Fee-Small business operation generic drug applicant | $159,079 |

## Biosimilar User Fees

| TYPE | FY 2017 | FY 2018 | CHANGE |
|---|---|---|---|
| Product Development | $203,810 | $227,213 | $23,403 (11.5%) |
| Application Reactivation | $407,620 | $454,426 | $46,806 (11.5%) |
| Application requiring clinical data | $2,038,100 | $1,746,745 | -$291,355 (-14.3%) |
| Application not requiring clinical data or supplement requiring clinical data | $1,019,050 | $873,373 | -$145,677 (-14.3%) |
| Establishment*** | $512,200 | N/A | N/A |
| Product*** | $97,750 | N/A | N/A |
| Program*** | N/A | $304,162 | N/A |

## Compounding Outsourcer User Fees

| TYPE | FY 2017 | FY 2018 | CHANGE |
|---|---|---|---|
| Establishment | $16,852 | $17,364 | $512 (3%) |
| Small Business Establishment | $5,279 | $5,364 | $85 (1.6%) |
| Reinspection | $15,837 | $16,093 | $256 (1.6%) |

*The PDUFA establishment fee was elimianted and the product fee was renamed the program fee in PDUFA VI.
**Prior approval supplement fees were eliminated in GDUFA II.
***The BsUFA establishment fee was eliminated and the product fee was renamed the program fee in BsUFA II.

*Source: Federal Register notices*

# Is ANDA Bolus Coming As Higher User Fees Loom?

**DERRICK GINGERY** derrick.gingery@informa.com

With less than a month before ANDA user fees increase substantially, there does not appear to be any evidence that sponsors clamoring for one final chance at filing under the cheaper rate – yet.

In August, the number of ANDAs submitted to FDA's Office of Generic Drugs remained steady at 73, the same total reported for the prior month, according to OGD generic drugs program activity data *(See chart)*

Submissions on average have been less than 71 per month since March, when a bolus of 197 was reported and attributed to sponsors in India clearing their books before the end of the country's calendar year. *(Also see "Generic Drug Puzzle: Why Did ANDA Submissions Spike Again?" - Pink Sheet, 11 Apr, 2017.)*

Another submission bolus seemed possible during the final two months of fiscal year 2017 if sponsors rushed to avoid paying a much more expensive user fee. An ANDA submitted Sept. 30 will be charged $70,480, while one submitted the next day (Oct. 1, the beginning of FY 2018) will be charged $171,823. *(Also see "Generic User Fee Hikes Could Disrupt US FDA Drug Pricing Campaign" - Pink Sheet, 28 Aug, 2017.)*

ANDA fees increased as part of the generic drug user fee program renewal, which shifted the revenue targets for application and facility fees. *(Also see "Generic Drug User Fees Will Jump More Than 50% In FY 2018" - Pink Sheet, 16 Oct, 2016.)*

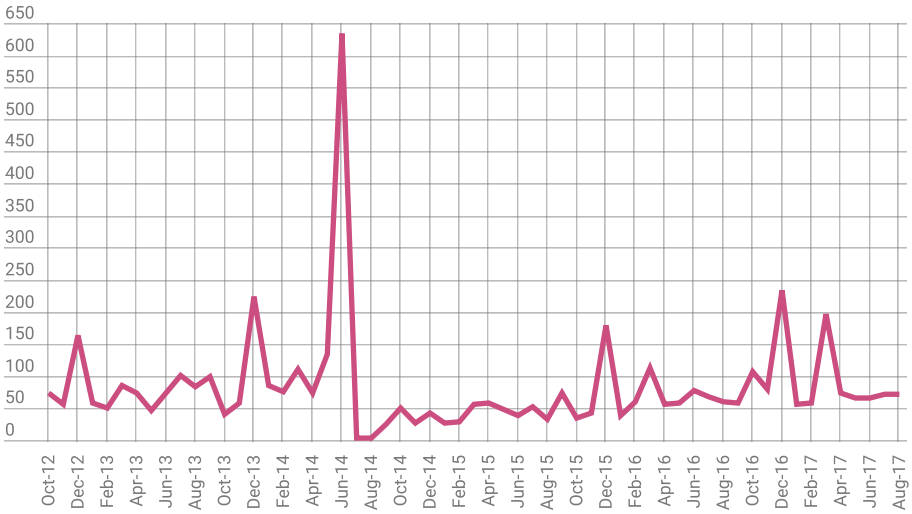
Given that margins on generics often are thin, sponsors may be motivated to try to beat the clock and avoid the higher fee.

However, David Gaugh, senior VP of sciences and regulatory affairs for the Association for Accessible Medicines, said that the trade organization is not expecting a submission rush because ANDA development moves along a regimented 18 to 36-month timeline.

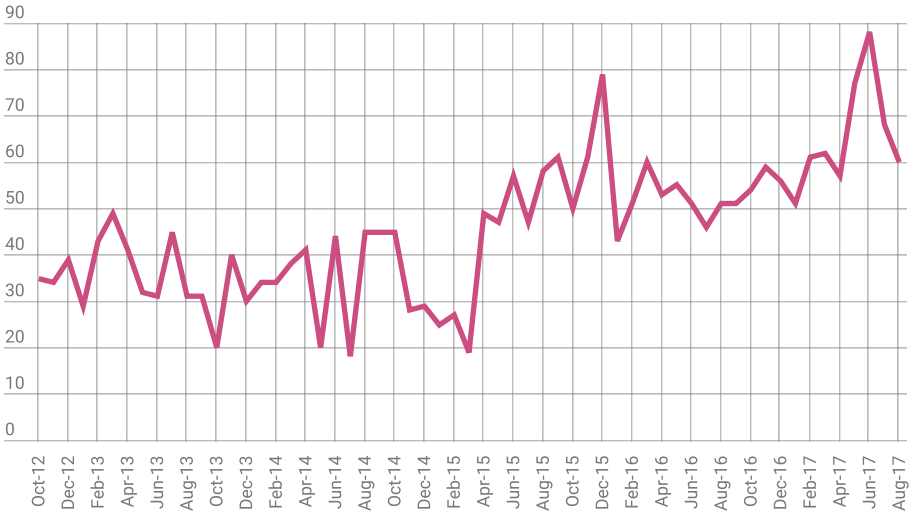
Since the new user fee rates were received a few weeks ago, it is unlikely

Given that margins on generics often are thin, sponsors may be motivated to try to beat the clock and avoid the higher fee.

## ANDA Submissions Remain Steady...




## ...And Approvals Continue Slide From Record High




Will an ANDA submission bolus materialize ahead of the Oct. 1 implementation of the FY 2018 user fees? There's no evidence of it yet with one month remaining in the fiscal year. ANDA approvals also remain near their FY 2017 average, but have retreated from the all-time high set in June.

*Source: FDA generic drug program activity report*

companies could speed up applications in time, Gaugh said. He also said the filing fee is a one-time charge and does not have the same effect on companies as the annual facility and program fees.

Robert Pollock, senior advisor and outside director to the board at Lachman Consultants, told the Pink Sheet that he was expecting a surge in September, although he said the fee announcement came late enough that many sponsors may not have time to react.

Pollock said sponsors will work to get as many applications to FDA as possible by Sept. 30 if it means they could save more than $101,000.

Brian Malkin, counsel at Arent Fox LLP, said that the user fee savings are an incentive for more submissions before Oct. 1, but added that it does not make sense to send an application before it is ready and risk a refuse-to-receive action.

Prior to GDUFA's launch in 2012, there was a rush of applications so sponsors could have them considered part of the statutory backlog. The fee associated with a backlogged application was lower than the new ANDA fee in FY 2013. *(Also see "Backlog Backfire: FDA Sees Increase In Pending Generic Applications At Deadline" - Pink Sheet, 15 Oct, 2012.)*

The most famous rush occurred in 2014, although it was not trying to avoid a fee increase. More than 600 applications were submitted in June that year, mostly to avoid new stability requirements that were going into effect. *(Also see "ANDA Avalanche: How Will FDA Deal With The 600 Received This Month?" - Pink Sheet, 30 Jun, 2014.)*

> Even without a September rush, the FY 2017 submission total will be the second largest of the GDUFA I five-year cycle.

## FY 2017 SUBMISSION TOTAL ALREADY SECOND-HIGHEST OF GDUFA ERA

Even without a September rush, the FY 2017 submission total will be the second-largest of the GDUFA I five-year cycle.

Through August, OGD received 1,090 ANDAs. It is 383 less than the FY 2014 total of 1,473, which included the rush to avoid the new stability requirements. The third largest total arrived in FY 2013. (*See table*).

Nearly half of all the submissions received in FY 2017 arrived during one of three months with higher than usual volume. One bolus arrived in October 2016, apparently as sponsors looked to take advantage of OGD's new 10-month review goal for most submissions. *(Also see "Another ANDA Submission Surge Begins" - Pink Sheet, 21 Nov, 2016.)*

Another bolus arrived in December 2016, the end of the calendar year for US and European sponsors. *(Also see "ANDA Stress Test: End-Of-Year Submission Bolus Pressures US FDA Review System" - Pink Sheet, 9 Jan, 2017.)*

## APPROVALS DROP SLIGHTLY, BUT MAINTAIN NEW LEVEL

OGD also saw its approval total decrease somewhat, although it continues to maintain the elevated average seen through most of FY 2017.

The agency reported 60 approvals in August, which is the lowest total since April. But it also is the sixth time in FY 2017 where there have been at least that many approvals in a single month. Prior to FY 2017, OGD approved 60 or more ANDAs in a month only four times.

The agency now is averaging 63 approvals per month, which is much higher than previous years. The total of 693 approvals through 11 months in FY 2017 in also represents the largest number of approvals in a fiscal year for the GDUFA era, with one month left to report.

As OGD's productivity improved in FY 2017, the agency has said it now is building up to its stride and can continue increasing approval totals. *(Also see "ANDA Approvals Break Record, May Set New Normal" - Pink Sheet, 10 Jul, 2017.)*

FDA also issued 155 complete response letters in August, which is the second highest monthly total of the year. There now have been 1,448 complete responses issued in FY 2017, the second-highest of the GDUFA era.

Unfortunately for industry, it remains the most common OGD action on an ANDA, especially for a first review cycle. *(Also see "Generic Drugs: First-Cycle Review Times Improve, But Hundreds Of ANDAs Still Pending" - Pink Sheet, 4 Jul, 2017.)*

## ANDA Submission Totals

| YEAR | TOTAL |
|---|---|
| FY 2013 | 968 |
| FY 2014 | 1,473 |
| FY 2015 | 539 |
| FY 2016 | 852 |
| FY 2017* | 1,090 |

**Data is through August only.*

*Published online September 11, 2017*

# FDA's Gottlieb Pushing 'Seamless' Clinical Trials For Faster Development

**MICHAEL CIPRIANO** michael.cipriano@informa.com

US FDA Commissioner Scott Gottlieb touted the use of combined-phase studies, or "seamless trials," by oncology sponsors, indicating that the method could become more widely adopted beyond the field of cancer drug development.

Speaking at the Regulatory Affairs Professionals Society Regulatory Convergence Conference Sept. 11 in Oxon Hill, Md., Gottlieb pointed to seamless trials as part of a broader plan for the agency to reduce drug development costs in the clinical phase.

Seamless trials involve one adaptive study where the phases are separated by interim looks. Gottlieb says such an approach saves time, reduces costs and the number of patients that have to be enrolled in a trial.

FDA has identified 40 active investigational new drug applications (INDs) for large first-in-human oncology trials that use the seamless trials, according to Gottlieb. Sponsors of these trials will usually add cohorts to investigate doses and activity in a variety of cancers.

"We've seen examples where this approach has allowed the rapid development of drugs in multiple different tumor types," Gottlieb said. "If we had to stop and start formal Phase II trials in each different organ system where a cancer arose, it could have been a protracted process. This approach is well suited to the kinds of drugs that are being developed now, where drugs intervene on common elements found across multiple kinds of disease states."

Gottlieb added that Oncology Center of Excellence (OCE) Director Rick Pazdur is looking at ways to better evaluate and incorporate the seamless trials into the agency's wider effort to "modernize" the approaches for drug development.

The use of seamless trials, however, may not stop with oncology drug development. Gottlieb noted that the approach has been used with a few newer immunological therapies, and that it may also be used in developing drugs that target specific molecular defects.

"Seamless designs are particularly advantageous for drugs that work in a variety of diseases, allowing rapid evaluation of the drug and potential approval under our accelerated approval pathway," Gottlieb said. "These new approaches are also highly consistent with the goals of the 21st Century Cures Act and the recently passed FDA Reauthorization Act."

Gottlieb went on to announce that the agency will "begin work" on at least ten new disease-specific development guidance documents over the next year. These will include areas of unmet medical need, such as Amyotrophic Lateral Sclerosis (ALS), he said.

The commissioner's remarks – which factor into the broader conversation of reducing drug prices by cutting down on development costs – come on the heels of the release of a Journal of the American Medical Association (JAMA) study, which found that the cost to successfully research and develop a cancer drugs is $648m, rather than $2.6bn usually cited by biopharma.

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"Seamless designs are particularly advantageous for drugs that work in a variety of diseases, allowing rapid evaluation of the drug and potential approval under our accelerated approval pathway," Gottlieb said.

Gottlieb acknowledged that although there is some criticism of cost estimates in developing a drug, he noted that the cost of capital is affected most by risk failure on top of the direct costs of research and development.

"As the risk of failure grows, entrepreneurs seek a higher potential return in order to support the initial investment," Gottlieb said. "The cost of capital is also significantly impacted by the time anticipated it will take to develop a new medicine."

Gottlieb's comments also come just days after he outlined the agency's plan on the pre-clinical front to make drug development more efficient. Speaking at Research America's National Health Research Forum Sept. 7, Gottlieb indicated certain second entry

therapies could require less pre-clinical data.

The commissioner will provide details on modernizing the role of FDA's medical staff Sept. 29 at the National Press Club.

### MODERNIZING DATA EVALUATION AND REVIEW

Gottlieb also outlined efforts the agency is taking to make evaluation of clinical data by sponsors, as well as review of data by FDA, more efficient.

He touted the use of more advanced computing tools and more sophisticated statistical methodologies, such as modeling and simulations, as a starting point. The commissioner, however, noted that access to such tools is limited, and that he is "directing an effort to try and increase our investment in these computing tools."

Gottlieb cited several benefits of advanced tools and methodologies, including their ability to evaluate safety and efficacy of different doses, help select the best dose for populations and subgroups and evaluate the reliability of surrogate endpoints.

"These tools are especially important to our use of modeling and simulation as a part of drug review, not only in our Division of Pharmacometrics, in the Office of Clinical Pharmacology, but across our review program," Gottlieb said. "Almost 100 percent of all new drug applications for new molecular entities have components of modeling and simulation embedded."

*Published online September 11, 2017*

# Efficacy Studies Not Enough? Consider GSK's Salford Lung Study As New Model

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The full results of the asthma part of the **GlaxoSmithKline PLC**'s Salford Lung Study have confirmed the beneficial effects of the once-daily inhaler combination *Relvar Ellipta* (fluticasone furoate/vilanterol, known as *Breo Ellipta* in the US) on asthma symptoms compared with usual care, in a "real-world" clinical effectiveness study that calls into question the dominance of double-blind randomized efficacy studies in supporting clinical guidelines and prescribing decisions that drive medicines' market share and, ultimately, company profits.

The lead investigator for the Salford Lung Study, Ashley Woodcock, professor of respiratory medicine at the University of Manchester, has thrown down the gauntlet for other pharma companies to follow GSK's lead. "This is the first study about real care, that is relevant to the patients in front of me, and [I] challenge other companies to do the same sort of study, because we need to treat asthma better," Woodcock told a press briefing held during the European Respiratory Society's annual meeting in Milan, Italy on Sept. 11.

Top-line results from the asthma part of the Salford Lung Study were announced earlier this year, and the full results of the study were presented at the ERS meeting and published in *The Lancet* online on the same day. *(Also see "Relvar/Breo "Real World" Asthma Benefits Help GSK – But Can't Remove Generic Threat" - Scrip, 8 May, 2017.)*


*Clean air is important to asthmatics; real world evidence may change clinical practice.*

> "I challenge other companies to do the same sort of study, because we need to treat asthma better."
> – Ashley Woodcock, lead investigator, Salford Lung Study

Results from patients from the chronic obstructive pulmonary disease (COPD) part of the study were announced last year. Relvar was developed in collaboration with **Innoviva Inc.** *(Also see "How To Successfully Strategize Real World Evidence For Market Access" - Scrip, 31 Oct, 2016.)*

What was particularly telling about the current Salford Lung Study findings in asthma patients in and around the northern UK city of Manchester was just how uncontrolled patients were on their usual medications. "I was astounded, when looking at the baseline data, to still see 90% of patients reporting they had asthma symptoms more than twice a week," remarked David Leather, GSK's medical vice president, respiratory franchise, who helped design the study with Woodcock.

A high proportion of patients also reported they used their reliever inhalers more than twice a week, had symptoms that limited their physical activity, or had

symptoms that affected them at night. "Asthma is not 'sorted', there is complacency about this disease," Leather added, a sentiment that may underline the continuing buzz of activity in developing new asthma therapies.

Woodcock called the Salford Lung Study groundbreaking in that it looked at disease symptoms that are key to controlling the disease, such as wheezing and tightness in the chest. These are symptoms that doctors ask about, are important to patients, and can change the way that patients are treated. "It's an effectiveness study, in a huge number of patients, with a questionnaire (the Asthma Control Test) taken face-to-face at the beginning and end of the year-long study, and with three telephone calls in-between. Otherwise, the patients' general practitioners were able to optimize therapy as they saw fit."

While noting that double-blind randomized studies in carefully selected patients were vital to the regulatory process, because of the need to know a new drug's physiological effects, the researchers said such "efficacy" studies were less informative about the role of medicines in the broader patient population. In contrast, "effectiveness studies are the sort of studies we need in the future to inform clinical guidelines," argued Woodcock.

That may be so, but the Salford Lung Study was a huge undertaking. Even with some of the heavy-lifting already done by GSK, other pharmaceutical companies may be put off from following the company's lead. The asthma-related part involved more than 4,000 patients at 74 primary care sites, that also required 132 community pharmacists to be trained in good clinical practice (at the start of the study Relvar was not yet approved for marketing); the design and updating of electronic patient healthcare records; and a team of doctors to monitor study participants daily for adverse events. It required the setting up of a consortium of collaborators that included academics, GPs, pharmacies, and NHS research groups, and is believed to have cost around £85m ($109.7m). *(Also see "Real World Evidence Is Critical To Pharma's Future: Can We Agree On What It Is?" - Scrip, 15 May, 2017.)*

> "Effectiveness studies are the sort of studies we need in the future to inform clinical guidelines." – Ashley Woodcock

Another unique element was that joint advice was sought from the UK regulator, the MHRA, and the health technology assessment body, the National Institute for health and care Excellence (NICE). "No other company had taken up this offer of joint advice, and it was a fascinating experience and very positive," reported Leather. "NICE said this was exactly the type of study they had been waiting for. The study protocol was approved at first pass, a visionary decision by the regulators," he added.

## STUDY RESULTS

So what were the final results of the Salford Lung Study in asthma patients? The researchers reported a statistically significant improvement in asthma symptoms when patients were treated with either of two doses of Relvar (92/22 µg or 184/22 µg of fluticasone/vilanterol) compared with usual care.

The study was designed as an open-label randomized study with minimal exclusion criteria, minimal intervention, and included a broad swathe of patients treated by GPs. Usual care included inhaled corticosteroids as monotherapy or in combination with long-acting beta-agonists. Symptom improvement was defined as an ACT total score greater or equal to 20 (scores range from poor at 5 to well controlled at 25), or an increase of ACT score of equal to or greater than 3.

For the primary endpoint at 24 weeks of therapy, 71% of patients on Relvar had achieved better control of their asthma, compared with 56% of patients on usual care, a statistically significant difference (odds ratio 2, 95% CI of 1.70 to 2.34; $p < 0.001$). Relvar was also associated with higher quality of life scores than patients on usual care ($p < 0.0001$), a greater decrease in work impairment ($p < 0.0001$), and a greater decrease in activity impairment ($p< 0.0001$). There was, however, no statistically significant difference between the two treatment groups with regard to asthma exacerbations.

In the intent-to-treat population, the incidence of serious adverse events were the same in both arms, 13%.

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# Can Patients Move The Rare Disease Treatment Needle In China?

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While China has a universal health insurance scheme covering over 95% of its 1.3bn people, the coverage is generally lacking for people with rare diseases such as spinal muscular atrophy (SMA), a progressive neurodegenerative disease.

The incidence rate for SMA is estimated to be one out of 6,000 newborns. And among adults, one of 50 adults is a SMA-causing gene carrier. If both partners carry the gene, the risk of having a SMA baby increases to 25%.

Until Dec.25, 2016, when **Biogen Inc.**'s *Spinraza* (nusinesen) gained US FDA approval, there was no approved treatment for the progressive disease, which causes patients to slowly lose control over their muscle movement due to damaged motor neurons. Babies with the condition can't do what normal infants do including crawling, walking, sitting up, and controlling head movement, despite having a normal emotional exchange with adults. Severe SMA cases have difficulties breathing and swallowing.

Compared to other rare diseases, the cause of SMA is well-defined and researchers hope to bring more therapies to the market soon. Companies such as **Roche** have been conducting several trials for RG7916, an oral small molecule jointly developed with PTC Therapeutics Inc. that modulates SMN2 splicing to increase expression of stable full-length SMN protein from the SMN2.

However, for Chinese SMA patients, there is no treatment available; Biogen has no plans to develop its therapy in China, and Roche's ongoing trials includes patients in the US, Canada, European countries, but not China, at least not thus far.

That has not deterred Chinese SMA patient advocacy groups from working towards bringing Spinraza to China, and having Roche include China in its trials.

"We have been in touch with the Chinese FDA, asking them to consider giving Spinraza a fast track review due to the urgent clinical need," head of Meier Advocacy Support Center for SMA Xin Huanping said in an interview on the sidelines of 12th ICORD Conference, held in Beijing Sept. 7-9.

"We also work with Roche to lobby for an expedited IND review, so the company can include Chinese patients in their global studies," she added.

The effort to bring in new orphan drugs to China is a multi-faced one. And despite the patient groups' eagerness, it's clearly up to each company to decide whether to apply for a new drug application (NDA) in China.

So far, few companies are willing to do so due to the lengthy regulatory process, lack of patent protection and market exclusivity associated with the orphan drug designation as in the US, and the absence of pricing and reimbursement incentives *(Also see "China Approves Merck Serono Orphan Drug Kuvan; Paves Way For More Orphan Drug R&D" - , 19 Jan, 2011.)*.

Orphan drug makers like **Shire PLC** and **CSL Behring** are hoping to nurture the market. Shire, for one, has helped kick-start a patient group for hereditary angioedema (HAE) in China, with a goal to improve diagnosis and early intervention.

## REGULATORY CONSIDERATION

Rare diseases are considered as a priority and the government gives certain regulatory benefits to treatments for such conditions, noted Gao Chenyan, director of Biologics Clinical Study at Center for Drug Evaluation (CDE), a new drug review wing of the China FDA.

As per China Drug Registration Administration Law issued in 2007, orphan drugs can be permitted reduced patient cases or a waiver from clinical study, if these therapies meet certain requirements. And a fast-track review option requires reviewers to shorten the review time from 90 work days to 80 days for clinical study (IND), and 120 work days for an NDA.

Following an update in 2009, drug makers can apply for a priority review for both new drugs and generics to treat rare diseases. In addition to the shortened review time and clinical trial waiver/patient number reduction, the CFDA also considers conditional approval, allowing the use of overseas study data, and extrapolation of studies, although the procedures are still being worked out.

"We usually publicly disclose drugs that are chosen for fast-track reviews, after the five-day disclosure period and if there are no objections, we will complete the fast-track review in the next month. So, there are roughly two months to complete the review for an IND," Gao told the conference attendees.

The timeframe is twice as fast compared with the required 80 work days.

> The cost consideration has many eyeing the Chinese market finding themselves struggling to move forward – Zhang Ye, head of Novartis Oncology China, Regulatory Affairs

Despite these initiatives, Xin of the SMA patient group is unsure that Chinese patients will be able to participate in the Roche multi-regional clinical study. Xin said that Roche, which filed a China IND in July, had previously set next April to compete the primary study. Comparatively, many countries have a shorter and more simplified approval process for INDs.

### MULTI-AGENCY APPROACH NEEDED

The absence of a clear rare diseases definition or a specific list, the lack of reimbursement and pricing incentives are other challenges facing drug makers eying the China market.

In the US, a rare disease is a condition affecting fewer than one out of 5,000 people. In Europe, they are "life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them." The term low prevalence is defined as generally fewer than one in 2,000.

Such definition is non-existent in China, and so is a rare disease list. The National Health and Family Planning Commission has not yet issued such a list.

Instead, patient groups have stepped in and started a patient registry, in a bid to create a national rare disease database mapping out the prevalence of most common rare conditions.

"From R&D to product launch, the process is still very long, and given a limited market size, the market entry of rare disease drugs to China is slow and companies are hesitating," said Zhang Ye, head of **Novartis AG** Oncology China Regulatory Affairs, at the conference.

To that end, a multi-agency approach is needed, she added, noting that regulators should waive trials and drug makers could include physicians in multi-regional studies to develop their diagnosis and treatment experience. Patient and physician support, though, is a must.

Another issue is post-marketing safety study, which manufacturers must consider before entering China. Zhang suggests that Chinese regulators should focus on safety, not efficacy to reduce cost and burden to drug makers.

Similarly, there is no dedicated legislation governing orphan drugs in China and products are subject to the same inspection rules of "three productions, three samples" and " all batch inspection " that has significantly increased the cost.

"The cost consideration has many eyeing the Chinese market finding themselves struggling to move forward," she said.

Additionally, the process of defining rare disease and outlining the list should be transparent and public, and the China FDA should establish an orphan drug office, suggested the executive.

*From the editors of PharmAsia News. Published online September 13, 2017*



# Industry Worries FDA Will See Drug GMP Violations Captured By Security Cameras

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The closed-circuit television footage referenced in the Form 483 report was clear: something FDA investigators weren't supposed to see was going on at Hetero Labs Ltd.'s drug manufacturing facility in Polepally Village, India.

But much about the video remains unclear to those who later read the Dec. 16 report, which FDA posted on its website: what the video was for, how FDA investigators got access to it, and what the implications were for other drug manufacturers.

Did it mean that firms should shut down their security video systems and erase their security video archives? Or at

Shutterstock: Vasin Lee

least establish video retention policies? These are some of the questions several industry sources have raised.

FDA's failure to mention the candid-camera incident in a subsequent warning letter only deepened the mystery. *(Also see "FDA Slams Hetero For Oversized Tablets And Dirty Equipment" - Pink Sheet, 1 Sep, 2017.)*

## SHREDDING THEIR REPUTATION?

Four days before two FDA investigators were scheduled to arrive at the Hetero Labs plant, CCTV archives they later reviewed showed someone bringing a document shredder into a document storage area.

Soon quality assurance technicians and others were using the shredder to destroy records.

The investigators observed "extensive shredding of what appears to be controlled documents and extensive signing of documents by QA."

The company left no record of what the workers destroyed, but the investigators said the color of the documents was "consistent with" batch manufacturing and packaging records.

The shredding continued until 1:13 am on Dec. 7, the day of the investigators' arrival.

## SECURITY OR LIABILITY?

The case of the Hetero Labs video is just one of several recent instances where CCTV archives formed the basis for Form 483 observations and warning letter citations.

Firms often archive CCTV video as part of their GMP systems, for example to document smoke studies and aseptic filling operations.

Such GMP video archives were behind an October 2016 warning letter's observations of gowned operators sitting on the floor and leaning on walls during filling operations in a cleanroom at Teva Pharmaceutical Works Pvt. Ltd.'s sterile injectables manufacturing facility in Godollo, Hungary. *(Also see "FDA's Teva Warning Letter Sets Agenda For Investigating, Remedying Sterility Failures" - Pink Sheet, 26 Oct, 2016.)*

Similarly, video recordings of aseptic operations that FDA officials reviewed during an inspection of Emcure Pharmaceuticals Ltd.'s facility in Hinjwadi, India, showed numerous infractions documented in a March 2016 warning letter, including operators crawling on their hands and knees under the filling line during routine aseptic filling operations.

But firms also operate extensive CCTV systems to ensure security of plant operations. These systems gather and store video from multiple locations throughout pharmaceutical manufacturing facilities. At plants that make controlled substances, they are omnipresent.

Decades ago, when these systems were based on videotape, they would loop back after a certain period, erasing what they had previously recorded.

But since electronic systems evolved and data storage costs declined, pharmaceutical companies have been storing vast archives of CCTV video.

Recent Form 483 reports and warning letters suggests that those video archives may be turning into a liability.

## A QUALITY/SECURITY GRAY AREA

It's not always clear from the wording of inspectional observations and citations how FDA obtained access to CCTV video, and under what authority.

The agency reviews records that are part of a facility's quality system. A video that documents cleanroom airflow patterns would qualify, while a plant security video would not.

But distinctions are sometimes blurred in actual practice. For example, some plants use security video to control access to aseptic processing facilities, making it part of the quality system.

Also, FDA has previously expanded the scope of records subject to inspection, and could perhaps do so with security video, some fear.

This has happened before with badge in/out records and even emails.

Sources told the Pink Sheet a quality manager's emails became part of one firm's quality management system in FDA's view because the manager relied on email rather than a custom software solution for investigations management.

## THE PROBLEM WITH OBSTRUCTING INSPECTIONS

There is a sense that section 707 of the July 2012 FDA Safety and Innovation Act may have left industry helpless to prevent FDA from expanding the types of records it reviews on inspection.

That provision allows FDA to deem all product adulterated at any establishment that agency personnel believe is delaying, denying, limiting or refusing inspection.

Industry has expressed concern over the way FDA has interpreted the provision in subsequent guidance, fearing that it would lead to inspectional scope creep. *(Also see "How FDA Will Use Its New Authority against Denying, Limiting or Refusing Inspections – And Why Industry is Still Worried" - Pink Sheet, 21 Nov, 2013.)(Also see "What Not To Do When An FDA Inspector Knocks At Your Door" - Pink Sheet, 27 Oct, 2014.)*

The key question is where the line should be drawn on the use of security, badging, email and other primarily non-GMP systems during inspections.

Some sources would advise firms to shut down their CCTV security systems so they couldn't be used for GMP citations. Others worry that FDA might view such a move with suspicion, wondering why the firm shut it off. Still others argue that GMP concerns shouldn't take precedence over the security concerns those systems were built to address.

There appears to be considerable interest in establishing some type of video retention policies, and it is possible that best practice recommendations will emerge in this area.

Meanwhile, sources say, two Chinese firms took no chances, shutting off their security video so it can't be used during GMP inspections.

## BIGGEST INNOVATION SINCE SECURITY LOG REVIEW

FDA and industry officials say the agency's apparent use of security video during GMP inspections reminds them of an earlier expansion of inspections to non-GMP records.

In March 2008, an investigator and a chemist from FDA found that certain equipment cleaning logs at Ranbaxy Laboratories Ltd.'s manufacturing facility in

Paonta Sahib, India, were contemporaneously signed as required.

However, the FDA team took the extra step of reviewing the security logs used to record entry and exit of personnel from the plant's Batamandi facility and found 14 instances in which the officials were not present on the days they purportedly signed the equipment cleaning logs.

Such security log reviews have since become a part of the agency's data integrity inspectional toolbox.

### WHO IS GOING TO SEE?

There is an episode of the late Julia Child's televised cooking show in which she gives some famous advice to aspiring chefs.

Clumps of a potato pancake Child flips in a non-stick skillet fall all over the kitchen range, and without skipping a beat, she scoops it up by hand and pats it back into the skillet, remarking, "You can always pick it up when you're alone in the kitchen. Who is going to see?"

The answer to her question, of course, is anyone who has tuned into the show – or who has access to the video archives.

*From the editors of the Gold Sheet. Published online September 10, 2017*

# RMAT Designation Enables Critical Manufacturing Discussions – FDA's Marks

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The new regenerative medicine advanced therapy designation is turning out to offer a major benefit of deeper regulatory interactions around manufacturing issues, according to Peter Marks, director of FDA's Center for Biological Evaluation and Research.

Like the US breakthrough designation, RMAT offers early and frequent opportunities for exchanges with regulators, with the goal of quicker reviews. But one difference is that the discussions in RMAT regulatory interactions are more focused on manufacturing issues, Marks said Sept. 11 at the Parenteral Drug Association's PDA/FDA Joint Regulatory Conference in Washington.

Congress established the new review pathway as part of the 21st Century Cures Act, which President Obama signed into law Dec. 13. FDA provided more details about the RMAT pathway for cell and gene therapies and tissue engineering products in a Jan. 19 notice. Sponsors have disclosed at least five products that have received RMAT designation.

Allowing more of a back-and-forth dialogue, as RMAT designation does, has turned out to be especially important for advanced therapies "because many of these products have very, very complicated manufacturing issues," Mark said.

For some of the more innovative advanced therapies, there's not much to say about efficacy, Marks pointed out. When there's a disease with no treatment and then something comes along where "people do 50% better on some outcome measure," he said it doesn't take a huge study to demonstrate efficacy.

However, Marks added, "the manufacturing considerations to make something the same time after time when you're talking about cell therapies, cell therapies on top of scaffolds, we're talking about now things that are drugs, devices, biologic combinations in some cases, and so discussion with the agency is quite helpful."

That said, the complexity of these products is "not a reason to throw up our hands and just say we can't define the process," Marks said.

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Industry faced similar challenges with small molecule drugs in the early 20th century, he said. "We didn't understand things anywhere near as well until after we had high performance liquid chromatography, gas chromatography, et cetera."

Yet before the advent of new analytical technologies, the industry was able to establish a basic level of control.

"In the regenerative medicine field, we shouldn't just decide we're going to set the bar really low, and then just say we don't have to worry about understanding manufacturing, because if we do that, the whole field will suffer," Marks said. "By understanding and pushing as much as we can to have defined processes, within reason, and balancing that, I think will drive the process forward."

*From the editors of the Gold Sheet. Published online September 12, 201*

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FIND IT AT: https://pink.pharmamedtechbi.com/manufacturing

# Exclusivity Provision Seems Likely To Surface In OTC Monograph Bill

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Members of the House Energy and Commerce Committee are interested in provisions to allow manufacturers periods of market exclusivity for some OTC monograph products as part of legislation to streamline the FDA system and establish a user fee program to support the agency's work in the area.

That was one of the take-aways from the Sept. 13 House Energy and Commerce Health Subcommittee hearing on OTC monograph reform. *(Also see "Legislators On OTC Monograph Reform: What Took You So Long?" - Pink Sheet, 14 Sep, 2017.)*

The hearing focused on a discussion draft principally authored by Energy and Commerce member Robert Latta, R-OH, to provide more flexibility for OTC monograph decisions and establish user fees. The draft currently does not include provisions to provide market exclusivity for sponsors of certain monograph proposals, but subcommittee ranking minority member Gene Green, D-TX, and Virginia Republican Morgan Griffith were among the members who asked whether the option should be included in potential legislation.

Suggesting OTC monograph legislation could become a vehicle for broader changes should it move forward, several subcommittee members also stated interest in establishing regulations for the agency's oversight of cosmetics manufacturing, including creating a user fee program. Development of regulations for the cosmetics industry has been a contentious issue between manufacturers and consumer health and environmental advocates. *(Also see "Beautycounter-Led Coalition Lobbies For Tighter Cosmetics Regulations" - Rose Sheet, 12 Sep, 2017.)*

Subcommittee Chairman Michael Burgess, R-TX, also used the hearing as an opportunity to ask Woodcock about the outlook for the return of OTC asthma inhalers *(see box below)*.

Should the subcommittee and other lawmakers decide on including a market exclusivity provision in potential monograph reform legislation, adding the language would have FDA's support.

Woodcock said "many folks want to talk about exclusivity," but FDA doesn't decide whether its regulations for drug and other product approvals include that incentive for manufacturers.

As with market exclusivity allowed for some products marketed as Rx-to-OTC switches, a piece of the Hatch-Waxman Act passed in 1984 to establish FDA's current system regulating generic manufacturing and encourage development of generics, exclusivity for approved monograph proposals would have to come

## WHITHER OTC ASTHMA INHALER?

Rep. Burgess a physician, remains interested in whether an OTC emergency asthma inhaler will become available again. In 2011, he questioned FDA's order to remove Primatene Mist from the market because the epinephrine product used ozone-depleting chlorofluorocarbons as a propellant.

"Let me make a plea, asthmatics do need an over-the-counter inhaler," Burgess said to close the subcommittee's questions for Woodcock.

The CDER director, however, could offer no comment other than noting that **Amphastar Pharmaceuticals Inc.**'s new drug application for Primatene Mist reformulated with hydrofluoroalkane as a propellant remains pending at the agency.

Amphastar has received two complete response letters from FDA on its NDA for a reformulated Primatene Mist, the second in December 2016 requested additional changes to the labeling and packaging and another human factor validation study to assess consumers' ability to use the actuated, or breath-triggered, inhalation aerosol without the guidance of a doctor or pharmacist. *(Also see "Primatene Mist CRL Underscores Challenges For OTC Asthma Treatments" - Pink Sheet, 4 Jan, 2017.)*

The CRL, roughly two years after the first in late 2014, likely added as much as 18 months to the time needed before Amphastar could re-launch the OTC product after receiving approval. FDA does not question epinephrine's safety, but the CRLs indicate the agency has heeded concerns of a joint panel of the Nonprescription Drugs and Pulmonary-Allergy Drugs advisory committees in 2014.

through legislation.

"I believe that is something that needs to be resolved," Woodcock said.

An early Senate discussion draft included authority for FDA to request human clinical trials for some monograph proposals and to make the manufacturer eligible for up to two-years market exclusivity. Any FDA-certified firms are allowed to make monograph drugs, which discourages some firms from investing in research and testing needed to substantiate GRASE for adding formulations or indications to a monograph. *(Also see "Two-Tier OTC Monograph Approach Could Come With User Fee Revamp" - Pink Sheet, 19 May, 2017.)*

"There hasn't been a lot of innovation," said Scott Melville, president of the Consumer Healthcare Products Association trade group.

While allowing market exclusivity for approvals of some of the more costly proposals could incentivize firms to invest in the research, Rep. Brett Guthrie, R-KY, pointed out the legislation will weigh manufacturers' benefits with consumers' health care costs.

"We must also be sure that our desire for innovation doesn't overcome our concern for patients' access," said Guthrie, who is full committee vice chairman.

*From the editors of the Tan Sheet.*
*Published online September 13, 2017*

# Legislators On OTC Monograph Reform: What Took You So Long?

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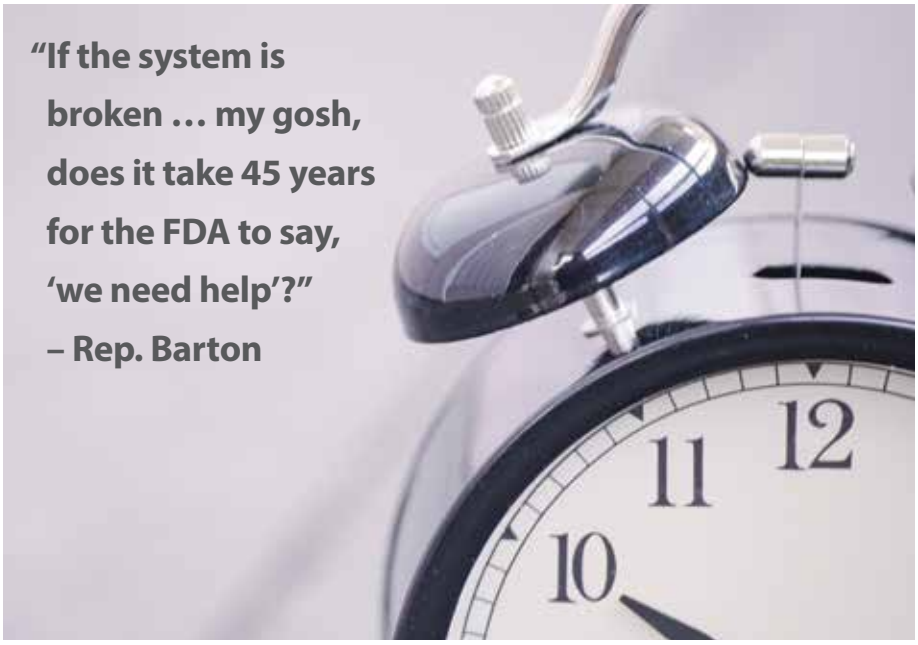
Members of a House subcommittee don't doubt whether FDA's OTC drug monograph program needs changes, but several want to know what took the agency so long to ask for help.

The Energy and Commerce Committee's Health subcommittee heard testimony on Sept. 13 from FDA drug center chief Janet Woodcock and industry stakeholders on monograph reform.

A discussion draft principally authored by Energy and Commerce member Robert Latta, R-OH, largely tracks a proposal negotiated by FDA's Center for Drug Evaluation and Research and drug firm representatives that takes monograph decisions out of the rulemaking arena, giving the agency authority to use administrative orders instead, and sets timelines for evaluations for each proposal as well as imposing fees of annual facility registrations and per-proposal payments. Subcommittee members appeared supportive of potentially expanding an eventual bill, including adding provisions to provide market exclusivity in some cases. *(Also see "Exclusivity Provision Seems Likely To Surface In OTC Monograph Bill" - Pink Sheet, 14 Sep, 2017.)*

Subcommittee members working with Latta on the monograph reform draft and the panel's majority and minority party leadership were joined by some 20 members from both parties during the hearing in expressing support for legislation that would improve the monograph process. Several members, however, also expressed surprise that they weren't apprised much sooner about problems that FDA officials say have hamstrung the monograph progress for much of its 40-plus years.

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"If the system is broken … my gosh, does it take 45 years for the FDA to say, 'we need help'?" said Rep. Joe Barton, R-TX.

Barton, vice chairman of the full committee, added that monograph logjam wasn't something FDA leadership wouldn't have known about. "Somebody there has known for a long, long time that this was a problem," he said.

Rep. Anna Eshoo, D-CA, struck a similar tone in her questions for Woodcock while also saying Congress should be absolved from any blame for the failure of the monograph program to fulfill its intended purpose since it was established in 1972.

"Not that [monograph reform] t doesn't need to be addressed, but it's strange to

me that it has been addressed," Eshoo said.

"Clearly this has been overlooked. My sense is that rests more with the FDA than with Congress," she added.

She also noted that cooperation between the subcommittee and FDA officials is a two-way process. "I'm talking about the relationship between the agency and Congress," Eshoo said.

Woodcock, speaking and fielding questions alone, did not excuse FDA for not asking Congress about changing the monograph process earlier, saying only that her and other officials' direct conversations with Capitol Hill are limited to testimony and other comments at hearings.

"We're not allowed to lobby Congress. That is my understanding," she said.

Woodcock did allow, though, that monograph reform has not been a priority legislative issue at the agency. "This is a rather obscure program and many people are unaware of it and how it works."

Higher FDA legislative priorities have included comprehensive food safety regulatory changes Congress passed in 2011 in addition to five-year authorizations of the agency's existing pharmaceutical and medical device user fee programs, with the latest, the FDA Reauthorization Act, coming in August. *(Also see "Implementing User Fees Should Be Lighter Lift For FDA This Time Around; Bill Heads To White House" - Pink Sheet, 3 Aug, 2017.)*

Subcommittee Chairman Michael Burgess, R-TX, acknowledged during the hearing that a Senate discussion for monograph reform had been circulated as a potential addition to FDARA, but lawmakers didn't have time to discuss incorporating the language before passing the bill as little time remained before the existing user fee streams would expire.

"We were pretty far down the road and I made the decision that nothing was going to deter us from getting the reauthorization across the finish line," Burgess said.

> Chairman Burgess didn't offer a timeline for the subcommittee's potential work on monograph reform legislation, but he clearly agrees change is needed.

The chairman didn't offer a timeline for the subcommittee's potential work on monograph reform legislation, but he clearly agrees with FDA's assessment that the program is bogged down by a public rulemaking process that turns any change, even urgent safety labeling, commonly into more than five and sometimes as many as 10 years of work.

"The regulatory agency needs to be much more agile than it currently is able to be under the monograph system," Burgess said.

## ADMINISTRATIVE ORDERS UNCLOG THE PROCESS

Woodcock, in written testimony and briefer remarks she stated at the hearing, reiterated to the subcommittee members the monograph program's plight she has described since FDA in 2014 launched its initiative to develop a proposal for improving the program. *(Also see "'Real Challenge' To Improve OTC Monograph Program Without User Fees – FDA" - Rose Sheet, 16 Jun, 2016.)*

"This process is frozen in 1972," she said.

"I think we have identified the problem," responded Rep. Buddy Carter, R-GA.

FDA launched the program in 1972 as a system for allowing OTC ingredients generally regarded as safe and effective for their intended uses to remain available and as a process for proposing additions of more ingredients or indications. A monograph states ingredients and formulations that can be used in nonprescription drugs for certain indications.

The program has been stalled for much of its 45 years, however, under a process that requires notice-and-comment rulemaking for any addition or change and that not only impedes adding OTC ingredients and indications, but also prevents FDA from efficiently responding to problems with monograph products on the market.

"We have really been hampered in responding rapidly to emerging safety issues," Woodcock said.

While the rulemaking process has proven cumbersome for the monograph process, the administrative order authority FDA wields for its oversight of and Rx and OTC drugs and medical devices approved through application processes should accelerate the monograph system, she said.

Administrative orders, the CDER director said, are "quite appropriate for scientific decision-making."

*From the editors of the Tan Sheet.*
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# Hepatic Safety Of Biogen Idec's Zinbryta Under Close Scrutiny In EU

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Biogen Idec's injectable multiple sclerosis drug, *Zinbryta* (daclizumab), is coming under scrutiny this week as the European Medicines Agency continues its review of the product's safety profile following reports of serious hepatic adverse reactions including the death of a patient from fulminant liver failure.

The review is being conducted by the EMA's Pharmacovigilance Risk Assessment Committee under an Article 20 referral initiated in summer by the European Commission. This week's meeting of the EMA's main scientific committee, the CHMP, will adopt a list of questions to be put to a special Scientific Advisory Group (SAG) regarding Zinbryta.

The commission has asked for a CHMP opinion by Nov. 30 at the latest as to whether the marketing authorization for the product should be maintained, varied, suspended or revoked. The commission will then take a final, legally binding decision based on that opinion.

SAGs are convened to provide advice on scientific and technical questions relating to medicines subject to referrals or other procedures, for example where there are complex technical issues involved, risk-minimization measures need to be scrutinized, or major post-authorization safety issues have arisen.

Participants in SAGs include core members of the group, EMA staff and experts, and the company can also send representatives to make a presentation and answer questions. The advice of the SAG is taken into account by the CHMP, whose final opinion will be based on the recommendation of the PRAC.

## LIVER ISSUES KNOWN

Zinbryta, which is co-promoted by Biogen and AbbVie, is no stranger to adverse liver reactions. Transaminase elevations and serious hepatic injury are known risks with the product. In the US, for example, the product has a boxed warning informing healthcare professionals that it can cause severe liver injury, including life-threatening and fatal events, as well as conditions like colitis, skin reactions and lymphadenopathy.

In the EU, several risk minimization measures were implemented after the drug's centralized approval in July 2016. These included monthly liver function monitoring, a recommended observation period for hepatic signs and symptoms, and specific actions to be taken on signals of liver injury, including discontinuation of treatment.

Many analysts had already warned that the liver issues and restrictive labeling could hinder the product's chances in the multiple sclerosis market, where it is competing against drugs such as Novartis's *Gilenya* (fingolimod) and Biogen's own *Tecfidera* (dimethyl fumarate), as well as Teva's *Copaxone* (glatiramer acetate).

Things took a turn for the worse in June this year when the commission was informed of the death from fulminant liver failure of a patient who had received four doses of Zinbryta in an ongoing observational study. The commission also pointed out that the first EU periodic safety update report (PSUR) on the drug assessed by the PRAC for the period May 27 to Nov. 26, 2016, included four cases of serious liver injury from clinical trials.


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The commission said there was a need to assess the product's benefit-risk balance and the adequacy of the risk-minimization measures, and triggered the Article 20 procedure. It also asked the EMA for its view on whether interim measures were needed.

## PROVISIONAL RESTRICTIONS

In July the PRAC decided that, pending the outcome of the safety review, the product could remain on the market but recommended a number of provisional measures be taken to minimize the risk of liver injury. It was, it said, "necessary to provisionally limit the use of daclizumab through restriction of the indication and through preventing its use in patients potentially predisposed to liver injury and provide further recommendations to healthcare professionals (HCPs) and patients in the management of this risk."

The PRAC recommended that the use of Zinbryta should be restricted to adult patients with highly active relapsing MS despite previous treatment with at least one disease modifying therapy (DMT) or with rapidly evolving severe relapsing disease who are unsuitable for treatment with other DMTs. Daclizumab should be contraindicated in patients with pre-existing hepatic disease or impairment "while the pattern of hepatotoxicity and possible mechanism of action is further investigated," it said.

The committee added that the warnings about monitoring for hepatic injury should be strengthened: "In the fatal case under review, the finding of normal serum transaminases levels prior to the dose of daclizumab did not prevent the occurrence of liver failure. Therefore, monitoring of serum transaminases levels should continue to be performed at least monthly and more frequently as clinically indicated, further, bilirubin levels should also be tested. In

addition, prompt recognition of signs and symptoms of liver injury is a key component of risk minimization for liver injury with daclizumab and these should be monitored in all patients."

These recommendations were implemented by a decision of the commission, but were subsequently revised "in view of discrepancies across sections of the summary of product characteristics," the EMA noted.

### ACTIONS ACROSS EUROPE

The restrictions have implications for patients in various countries such as the UK, where the HTA body, the National Institute for Health and Care Excellence (NICE), had said earlier this year that Zinbryta should be made available on the National Health Service in England and Wales.

Following the EMA action, NICE said that the restrictions represented a more limited indication than originally appraised in its technology appraisal guidance. People with active relapsing-remitting MS previously treated with disease-modifying therapy and whose disease was not "highly active" would "no longer be eligible for treatment because of the EMA's provisional restrictions," it said, adding that NICE would "review the recommendations on daclizumab and amend them if appropriate when the EMA concludes its review."

In France, the HTA body Haute Autorité de Santé said in January this year that no clinical benefit of Zinbryta had been shown in the treatment of relapsing forms of MS. While the product had "substantial" medical benefit in MS, it said it "does not provide clinical added value in the current management strategy for relapsing forms of multiple sclerosis which includes clinically relevant comparators."

Biogen had not responded to a request for comment at the time of publication.

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# FDA's NDA And BLA Approvals: Aliqopa, Mvasi

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 Biologics** | | | | |
| Bayer | *Aliqopa* (copanlisib) | Treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies. | | 9/14/2017 |
| Amgen | *Mvasi* (bevacizumab-awwb) | Biosimilar to Avastin to treat patients with metastatic colorectal cancer, with intravenous 5 fluorouracil–based chemotherapy for first or second line treatment; metastatic colorectal cancer, with fluoropyrimidine irinotecan or fluoropyrimidine oxaliplatin-based chemotherapy for second line treatment in patients who have progressed on a first line bevacizumab product-containing regimen; non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease; glioblastoma, as a single agent for adult patients with progressive disease following prior therapy; metastatic renal cell carcinoma with interferon alfa; cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease. | | 9/14/2017 |

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

# Opioid Cough Restrictions: Pediatric Use, And Postmarket Studies, Likely Limited

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"We'd probably be reducing the amount of prescriptions of codeine and hydrocodone by a relatively small amount, but that's still something that we view as better than nothing." – FDA's Alexander

A US FDA advisory committee's strong recommendation against use of opioid-containing antitussives for pediatric cough suggests sponsors of such products are likely to face further labeling restrictions but also could be relieved of some postmarketing study requirements.

In a series of votes Sept. 11, the Pediatric Advisory Committee overwhelmingly concluded that the benefit/ risk profiles of codeine and hydrocodone are not favorable for treating cough associated with allergies or colds in pediatric patients, or more generally for the treatment of pediatric cough. (*See box, p. 22.*)

Panelists echoed a common refrain in explaining the reasoning for their votes. There exists little to no evidence that codeine and hydrocodone, which were deemed effective pursuant to the Drug Efficacy Study Implementation (DESI) process in the 1980s, provide any benefit in treating pediatric cough related to cold or allergy under modern regulatory standards, committee members said. In addition, the drugs carry known risks, including fatal respiratory depression, addiction and abuse.

Some panelists did draw a distinction between hydrocodone and codeine, viewing the latter as potentially more dangerous due to the risk of ultra-rapid metabolism in some patients. Nevertheless, they repeatedly referred to the use of the two drugs to treat pediatric cough as "antiquated," inconsistent with current practice guidelines and standard of care, and unsupported by high-quality evidence.

"We have effective alternatives that have been tested. We have a disease with a very low risk profile, yet we're looking at a drug that has a risk of death," said Christy Turer, a pediatrician at University of Texas-Southwestern Medical Center. "That to me seems very disproportionate that the risk of the drug far exceeds the benefit it would provide to the patient."

Although the meeting was focused on the pediatric claims for opioid-containing antitussives, Turer suggested the agency may want to consider removing the products from the market entirely.

"I think it's pretty clear that if we were faced with [a new drug application] today based on what we know, we would not vote to recommend approval of codeine-containing cough syrup for kids," said Steven Meisel, system director of medication safety at Fairview Health Services.

## WEIGHING THE PUBLIC HEALTH IMPACTS

Panelists and even FDA staff acknowledged that removing the pediatric information from labeling would likely amount to a very small step in the effort to combat opioid abuse and misuse, but they considered it one worth taking.

Codeine- and hydrocodone-containing antitussives account for only a small portion of outpatient Rx drugs dispensed for pediatric cough, representing 471,000 and 65,000 prescriptions, respectively, in 2016, according to data presented by FDA. In comparison, 4.9 million prescriptions were dispensed for pediatric use of dextromethorphan-containing products.

"If what we're doing is simply removing the indication for children – we've already seen the data with regard to drug utilization – we'd probably be reducing the amount of prescriptions of codeine and hydrocodone by a relatively small amount, but that's still something that we view as better than nothing," said John Alexander, deputy director of FDA's Division of Pediatric and Maternal Health.

"At the same time … with the availability of all the medications and certainly the amount that's prescribed for adults … we probably wouldn't be having great impact on what's available for an adolescent to get to that's in the medicine cabinet," Alexander said.

Nevertheless, some panelists saw the pediatric cough indications as a good place to start.

"I do believe that there is a tide turn that needs to be reached where we start to think differently about opioid substances, and there is no better place in my mind than for that to be in the pediatric population," said pediatrician Jennifer Plumb, University of Utah. "Cough is not the right indication for opioids."

## UCB PUSHES FOR NARROWER INDICATION

The panel's recommendation marked the second time in the last two years that an advisory committee has urged FDA to contraindicate use of codeine-containing

cough products in patients younger than 18 years old.

In December 2015, most advisory committee members favored contraindicating codeine-containing products for any pain management and for treatment of cough in patients younger than age 18. Instead, FDA contraindicated use in children younger than 12 years old and added warnings against use in adolescents at heightened risk for respiratory depression. *(Also see "Opioids: FDA Eyes Better Prescriber Education, But Academics Urge Promotion Crackdown" - Pink Sheet, 20 Apr, 2017.)*

Currently, most codeine-containing antitussives are contraindicated in patients younger than 12 years, although some newer products lack a pediatric indication entirely pending completion of required postmarketing studies. Some older hydrocodone cough/cold combinations have dosing information for children down to age six years, while newer products do not because labeling updates are pending the completion of pediatric studies.

The advisory committee meeting was unusual in that the panel heard formal presentations from two industry sponsors who supported new restrictions on pediatric use.

**UCB SA** has submitted a labeling supplement to contraindicate use of *Tussionex* (hydrocodone/chlorpheniramine) for patients under 18 years of age. The product currently is indicated for relief of cough and upper respiratory symptoms associated with allergy or cold in adults and children six years and older. *(Also see "Opioids For Pediatric Cough: UCB Seeks Limits, Pressuring Other Sponsors" - Pink Sheet, 10 Sep, 2017.)*

> "Our comprehensive review revealed no new safety concerns but also did not demonstrate any robust evidence for efficacy in the relief of cough or upper respiratory symptoms in children." – UCB's Sloan

Victor Sloan, vice president and development strategy lead at UCB, said the company conducted a review of Tussionex's benefit/risk profile that considered modern pharmacovigilance methods, changes in clinical practice, and review of literature using up-to-date methods.

Since Tussionex's approval in 1987, the company has received 391 individual safety case reports, 35 of which were in children. Of these 35 cases, 18 were serious, 11 occurred in children under age six years, and there were 10 fatal events. All of the 35 cases occurred prior to the company's introduction of a unit-of-use presentation.

"Current best practices and evidence suggest that the best treatment for acute cough in children is management of the underlying disorder," Sloan said. "Our comprehensive review revealed no new safety concerns but also did not demonstrate any robust evidence for efficacy in the relief of cough or upper respiratory symptoms in children."

"Applying modern evidence and pharmacovigilance methods, we determined that the benefit/risk ratio for Tussionex in children was no longer favorable," he said. "Even though the risk minimization measures – contraindication under six and unit of use – reduced serious and fatal cases, cases still occurred."

Sloan's presentation struck a chord with some panelists.

Given that UCB wants to contraindicate Tussionex use in patients under age 18 years, "who are we to tell the manufacturer, 'No, you've got to still market it to kids,'" Meisel said. "If the manufacturer believes that the benefit/risk profile is no longer favorable, then it seems to me I'd be hard-pressed to suggest that indeed it is."

## IMPACT ON PREA REQUIREMENTS

Any further labeling restrictions around pediatric use of the codeine and hydrocodone products could have ramifications for postmarketing studies required under the Pediatric Research Equity Act (PREA).

Peter Starke, association director for labeling in the Division of Pulmonary, Allergy and Rheumatology Products (DPARP), said FDA has been discussing internally what to do about the PREA requirements for recently approved opioid antitussive combinations, particularly in light of the 2015 advisory committee recommendations. "Your input will also help us to make decisions about the PREA requirements for these drug products."

On this issue, the panel heard a presentation from Leonard Lawrence, manager of regulatory and clinical affairs at Sovereign Pharmaceuticals.

Sovereign holds the NDA for *Obredon* (hydrocodone/guaifenesin) oral solution,

## ADVISORY COMMITTEE VOTES

1. Is the benefit/risk favorable for use of prescription codeine cough suppressants for treatment of cough associated with allergy or the common cold in pediatric patients 12 to <18 years of age? **Y – 0, N - 24**

2. Is the benefit/risk favorable for use of hydrocodone cough suppressants for treatment of cough associated with allergy or the common cold in pediatric patients:
   - 6 to <12 years of age? **Y – 1, N - 23**
   - 12 to <18 years of age? **Y – 1, N - 23**

3. Is the benefit/risk favorable for use of prescription opioid cough suppressants for treatment of cough in pediatric patients? **Y – 2, N – 21, Abstain - 1**

which was approved in November 2014. It is one of six products containing codeine or hydrocodone that have outstanding pediatric study requirements under PREA and are labeled only for use in adults 18 years and older pending results from pediatric trials.

Pursuant to the Obredon approval letter, Sovereign was to conduct a pharmacokinetic (PK) study in patients ages 6-17 years and submit a final report by March 2017. The agency also required a Phase IV safety study in the same pediatric age range, with a final report due in 2022.

Sovereign has not started the required postmarketing studies because it lacked the necessary funds, Lawrence said in an interview with the Pink Sheet. In addition, Sovereign currently is not selling Obredon because the company failed to market it properly after hydrocodone was reclassified as a Schedule II substance, he said.

Sovereign is looking to revive the drug, which it has renamed *Ayzrol*, with help from another company. However, the drug will soon be listed in FDA's Orange Book as discontinued, he said.

Nevertheless, Lawrence urged FDA and the advisory committee to reconsider and revoke the PREA requirement for all pediatric age groups, citing safety and ethical considerations. He also said the company would support making stronger statements on labeling about use of hydrocodone in the pediatric population.

"Sovereign contends that performing the PREA-required PK study and safety studies is inappropriate and places both children and adolescents at undue risk," he said. "There is no evidence that the conduct of such a study would provide any data that would add value to the contraindication and the warnings that FDA already has implemented."

Sovereign also is concerned that an institutional review board "would not be able to approve the proposed studies give [the] additional safeguards required for children in clinical investigations," he said. "Additionally, if these studies were to be performed and an adverse reaction or death occurred, is FDA prepared to take full financial responsibility because the agency has required that these studies be performed? This full responsibility needs to be provided by the agency in writing prior to the opioid drug dosed to the pediatric populations. I know this is nonstandard, but you are putting a population at significant risk doing this type of studies."

Vanderbilt University pediatrician Stephen Patrick asked FDA what would happen to the PREA study requirements for opioid antitussives if their use in pediatric patients were further restricted.

Sally Seymour, DPARP's deputy director for safety, said that when the codeine-based products were contraindicated in children younger than 12 years, "we asked the companies to amend their pediatric studies so that they're only doing them in children 12 and older, so we would not ask for them in that contraindicated age group."

If FDA ultimately contraindicated the codeine or hydrocodone products in patients younger than 18 years, "I think it would be a very unusual situation that we would ask for pediatric studies in … an age group we didn't think they should be used."

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# Novartis Set 'Responsible' Price For Kymriah, Express Scripts Says

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**Novartis AG**'s approach to pricing its recently approved chimeric antigen receptor T-cell therapy for childhood leukemia, *Kymriah* (tisagenlecleucel), has drawn praise from drug pricing critic Steve Miller, chief medical officer at the pharmacy benefit manager **Express Scripts Holding Co.**

When Kymriah was approved Aug. 30, Novartis announced the one-time, single-administration treatment would have a list price of $475,000. The price was generally in line with (indeed even somewhat below) most investors' expectations. *(Also see "Novartis Beats CAR-T Competitors To The Pricing Punch With Kymriah Approval" - Scrip, 31 Aug, 2017.)*

"I think Novartis has been pretty responsible in how they approached this," Miller observed at a Sept. 12 policy discussion on gene therapy sponsored by The Hill. "We've been very aggressive on drug pricing and call out when we think someone has been

over-pricing their drugs." But "gene therapy is a totally different ball game and we're going to have to think about it differently."

Miller suggested comparing the gene therapy's cost and outcomes with the current standard of care. "When you look at cure rates in these kids and the cost of stem cell transplant versus the cure rates and cost with CAR-T therapy, there's not a big difference in cost. But there's a huge difference in outcomes," he pointed out. "That's worth a premium in the marketplace."

Miller also suggested **Spark Therapeutics Inc.** could take a similar approach to pricing its gene therapy for hemophilia. The company has two candidates in development: SPK 9001, which is being co-developed with **Pfizer Inc.**, is in Phase I//II testing in hemophilia B, and SPK-8001 is in Phase I/II for hemophilia A.

However, hemophilia is a more common disease and so the cost of the gene therapy could reasonably be set much higher than Kymriah because cost offsets would be much higher, he indicated. That raises the issue of how payers will manage the costs.

"Hemophilia costs the US about $150,000 to $200,000 per patient per year. So the medical offset for that is really easy," Miller said. But the problem is, "Do you pay for it all up front? Do you amortize it over the course of years? How do you do value-based contracting? How do you handle portability if a patient changes from one insurer to another over time?"

Express Scripts is "working with … Novartis and Spark and others because not only do we need a revolution in the science of the drug, we need a revolution in the science of reimbursement for drugs," he added.

In its current responsibilities as a pharmacy benefit manager Express Scripts would not be directly involved in reimbursing gene therapies administered by health care professionals in the hospital. PBMs generally manage drugs dispensed for self-administration through retail pharmacies.

However, the PBM may be positioning itself for a broader role in covering novel treatments. "High cost medicines – gene therapies or otherwise – strain payers' budgets. Express Scripts believes there may be ways we can help improve affordability of gene therapies, and we are currently evaluating some potential strategies to do so," a company spokesman said in an email.



PBMS generally are not directly involved in reimbursement therapies administere in settings like a hospital but Express Scripts may be positioning itself for a broader role.

"The main role of PBMs, of course, is to manage the rest of the pharmacy benefit so that payers can afford breakthrough treatments, even those that come to the market with an exceedingly high price," he added.

## AMORTIZED PAYMENTS TIED TO OUTCOMES

In the case of a gene therapy treatment for hemophilia, Miller outlined a scenario where payments could be amortized and tied to the durability of benefit over time.

If the developer charges $1m for a treatment (and assuming the management of hemophilia patients already cost payers $150,000 a year), "wouldn't it be great if the payer … paid $100,000 up front and $100,000 a year for 10 years? If the drug stopped working, then you'd stop reimbursing the biotech company. So it would be a value-based" arrangement, he pointed out.

Such an arrangement might be possible in the private sector but not currently in government-sponsored insurance like Medicare or Medicaid, Miller noted. However, the Centers for Medicare and Medicaid Services has announced it is interested in outcomes-based payments for gene therapies, starting with Novartis' Kymriah. *(Also see "Novartis Begins CAR-T Payment Experiments With Outcomes-Based Contract With CMS" - Pink Sheet, 30 Aug, 2017.)* Experiments in novel contracts for gene therapies could be launched through the CMS Center for Medicare and Medicaid Innovation.

The idea of amortized payments for gene therapy was also proposed by Rep. Patrick Meehan, R-Penn., at the meeting.

"We're making [payment] decisions today for a therapy you say will cure this disease. But we don't know 30 years down the road" if it will still work, Meehan, a member of the House Ways and Means Committee, pointed out. "Some cancers could be in remission for nine years and can come back."

So maybe a manufacturer and payer "both agree to something like a mortgage that you are paid over a period of time, as long as that individual continues to live disease-free from the state you've treated." There are different ways to approach this and one would be for payers to "go out to the finance markets and have somebody up-front that cost," he noted. "People are going to have to be creative about how you get to a solution."

*Published online September 13, 201*

# Is Europe's BeNeLuxA Coalition Moving Too Fast?

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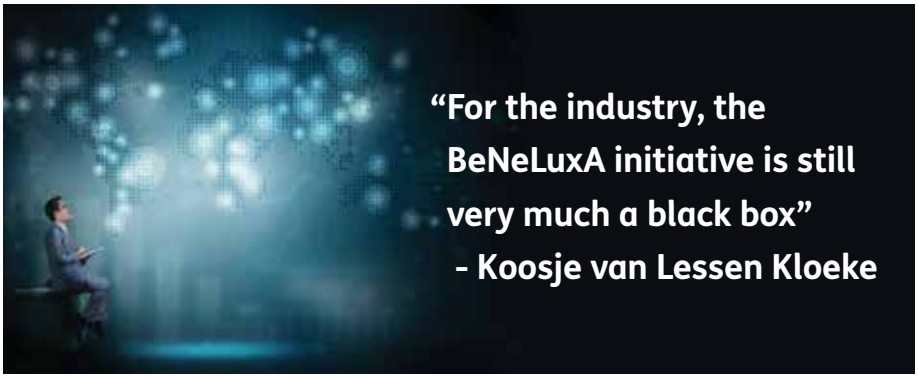
The BeNeLuxA coalition of smaller European countries that is working to improve access to medicines is still a big unknown for the industry and its expansion could be happening too fast. That's the warning from Dutch lawyer Koosje van Lessen Kloeke.

The initiative currently comprises four small EU markets, Belgium, the Netherlands, Luxembourg and Austria, but it could be set to expand to take in much bigger markets, such as France, as well as some countries outside of the EU. *(Also see "France In Talks With BeNeLuxA Access To Meds Coalition; Group Plans Expansion Beyond EU" - Pink Sheet, 7 Sep, 2017.)* However, "for the industry, the BeNeLuxA initiative is still very much a black box," warns Koosje van Lessen Kloeke, a partner at the Dutch law firm Leijnse Artz and lecturer in regulatory life sciences. Van Lessen Kloeke welcomes the launch of the initiative's new website as a good first step towards greater transparency, but notes that there is as yet little information available on the site. *(Also see "BeNeLuxA Website Goes Live" - Pink Sheet, 7 Sep, 2017.)*,

"I find it interesting that the Initiative is already talking about expanding the collaboration with other partners from the EU/EEA and even partners from non-EU countries, since we are still at a learning stage and the first pilots have not yet been evaluated," van Lessen Kloeke told the *Pink Sheet*.

Van Lessen Kloeke wants to see greater input from industry in the initiative. "Developing a sustainable collaboration requires commitment from all the parties involved and mutual trust. I think that the collaboration would benefit from a constructive dialogue with the industry and an evaluation of the first pilots with all the parties involved, including pharma companies".

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## CONSEQUENCES

Among other things, the coalition is looking to conduct joint pricing negotiations with drug companies. This area is bound to get attention but, van Lessen Kloeke warns, the initiative's work on joint health technology assessment and horizon scanning could have greater ramifications for companies. Pricing and reimbursement negotiations require company involvement, but joint HTA and horizon scanning initiatives may not, she points out. If companies are not able to participate in the processes they will have very little influence on the outcomes.

Questions remain around confidentiality and there could be considerable impact on companies, particularly if the initiative expands. As yet it is unclear what exactly countries will share and whether this will include commercially confidential, or other sensitive information that might be "disclosed in good faith" by local affiliates. "Could this information be shared with other countries, unbeknown to the company that provided the information? Are multinational companies always aware of information that is shared on a country level? And are company affiliates aware of information that other affiliates share?" van Lessen Kloeke says.

Van Lessen Kloeke also wants to see collaborating countries develop a common understanding regarding key concepts, such as therapeutic value, added therapeutic value and even price and whether this means net price or gross price. "Starting points for the pharmaco-therapeutic assessment have to be similar in the countries involved, and any differences, for example, in national clinical practice or criteria have to be identified beforehand. I highly doubt that this is currently the case."

## LEGAL QUERIES

Any expansion of the coalition is likely to lead to greater legal debate, both nationally and internationally, says van Lessen Kloeke. For example, she points out that in the Netherlands there is no legal basis for negotiations or managed entry agreements between companies and the ministry of health. Furthermore, it is possible that the activities in which it is involved – information sharing, joint horizon scanning, HTA and pricing and reimbursement negations – could fall within the scope of the Transparency Directive (Council Directive 89/105/EEC) and could impact the EU's single market. This directive tries to ensure that government pricing and reimbursement systems are transparent and sets out the procedural requirements for verifying whether national pricing and reimbursement decisions create obstacles to pharma trade within the single market.

The BeNeLuxA initiative has so far completed four pilots. One involved the joint assessment of and price negotiations for Vertex's cystic fibrosis treatment, *Orkambi* (lumacaftor/ivacaftor). Three other pilots involved joint HTAs, after which participating countries decided against pursuing pricing talks. Further details on the pilots have not been disclosed, in line with agreements in place between the firms and the coalition. *(Also see "New BeNeLuxA Access To Meds Initiative Pilots Are Under Way" - Pink Sheet, 1 Sep, 2017.)*

*From the editors of Scrip Regulatory Affairs. Published online September 14, 201*

# Recent And Upcoming FDA Advisory Committee Meetings

| TOPIC | ADVISORY COMMITTEE | DATE |
|---|---|---|
| Current practice and benefit/risk considerations for use of prescription opioid products containing hydrocodone or codeine for the treatment of cough in pediatric patients | Pediatric | Sept. 11 |
| Pediatric-focused safety reviews, as mandated by the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, for various products | Pediatric | Sept. 12 |
| GlaxoSmithKline's zoster vaccine recombinant, adjuvanted | Vaccines and Related Biological Products | Sept. 13 |
| Results from a clinical study of Purdue Pharma's *Butrans* (buprenorphine) transdermal system in patients ages 7-16 years old for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate | Anesthetic and Analgesic Drug Products/Drug Safety and Risk Management | Sept. 14 |
| Pfizer's *Sutent* (sunitinib) for adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma following nephrectomy | Oncologic Drugs | Sept. 19 |
| PTC Therapeutics' *Translarna* (ataluren oral suspension) for treatment of patients with dystrophinopathy due to a nonsense mutation in the dystrophin gene | Peripheral and Central Nervous System Drugs | Sept. 28 |
| Selection of strains to be included in an influenza virus vaccine for the 2018 southern hemisphere influenza season | Vaccines and Related Biological Products | Oct. 4 (teleconference) |
| Spark Therapeutics' *Luxturna* (voretigene neparvovec) for treatment of vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy | Cellular, Tissue, and Gene Therapies | Oct. 12 |

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