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Multi-Company, Multi-Product Clinical Trials On The Cards For Rare Pediatric Diseases

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Developers of medicines for rare diseases in children should consider the possibility of testing their products in multi-company, multi-product studies, according to a joint proposal by regulators in the US and the EU.

The proposal, published on July 3, seeks to facilitate the development of medicines for rare pediatric diseases, an area where there is typically only a small number of patients available to take part in trials.

Drug sponsors should also make better use of extrapolating available clinical data, the Food and Drug Administration and the European Medicines Agency say. They should extrapolate available data, including through appropriate modeling and simulation techniques, to predict how their product might work in children and adolescents based on studies conducted in adults or other pediatric populations.

The proposal, published as a "strategic collaborative approach" document, focuses on drug development for Gaucher disease, but its underlying principles can apply to other rare diseases in children, the agencies say.

By testing the safety and efficacy of medicines developed by different companies in one single trial (so-called multi-arm, multi-company clinical trials), the same control arm would be used to compare more than one medicine under evaluation, the EMA explained. This would facilitate the clinical testing of drugs and reduce the total number of children included in trials.

LIMITATIONS OF SIMULTANEOUS DRUG DEVELOPMENT

The regulators recognize there are inherent limitations and challenges to conducting simultaneous drug development programs. Legal and regulatory issues concerning such things as governance and funding of a study (sponsorship), and eligibility for EU and US pediatric reward/ incentives, would need to be dealt with on a case-by-case basis.

With regard to the strategic collaborative approach for Gaucher disease, developers who wish to use the new approach in their development plan are advised to seek scientific advice either from the EMA or the FDA separately, or request parallel scientific advice from the two regulatory authorities. The new document should not be interpreted as formal guidance, the agencies say.

"Specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the sponsors and the regulatory agency," the regulators explain in a document comprising stakeholder comments on a draft version of the new approach.

CONTINUED ON PAGE 4

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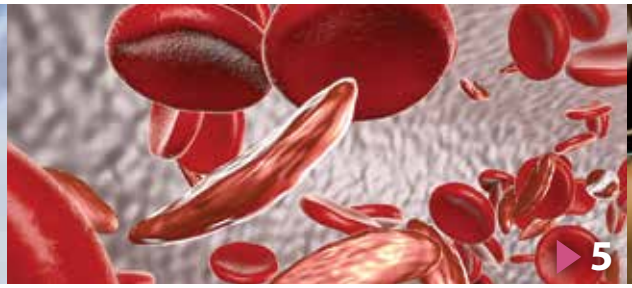
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Tackling The High Rejection Rate For Invented Names In The EU

https://pink.pharmamedtechbi.com/PS121042

Despite a revamp of the EU guideline on choosing a brand name for a new drug, more names continue to be rejected than accepted. Alexios Skarlatos, the chair of EMA's Name Review Group, and Jose Ferrero, a scientific administrator at the agency, discuss what can be done to improve things. It's a lot more complex than you might think.

ICER Eyes Gene Therapy: Category-wide Policy In Works As Spark Moves To Approval

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Institute for Clinical and Economic Review launches value assessment of Spark's blindness treatment vortigene neparvovec, the first gene therapy likely to reach the US market, in an effort to facilitate development of coverage policies.

Brazil's Anvisa Enjoys Industry Support Despite Regulatory Changes, Low Funding

https://pink.pharmamedtechbi.com/PS121017

Brazil's regulatory agency must now approve drug applications in specified timeframes, despite lack of resources; industry nevertheless sees a bright future for Anvisa and other agencies in region.

Generic Drugs: First-Cycle Review Times Improve, But Hundreds Of ANDAs Still Pending

https://pink.pharmamedtechbi.com/PS121014

US FDA cut first-cycle review time 46% between fiscal year 2013 and FY 2015, but more than 900 ANDAs still awaited review by end of 2016.

Insulin Market Competition: Payers Watching FDA 'Transition' Policy

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FDA policies around the upcoming regulatory reclassification of insulins as biologics may impact payers' ability to leverage competition and pricing in the market, Express Scripts suggests.

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A range of other conditions would benefit from the new collaborative approach, according to one of the stakeholders' comments. These include hepatitis C and Duchenne muscular dystrophy, the stakeholder said, adding that the approach "would be relevant for Fabry Disease and Pompe's Disease where a number of new treatments are on the horizon."

EFPIA said that questions are likely to include governance and funding of a study, eligibility for and timing of pediatric reward/incentives, and the potential for a PIP (EU pediatric investigation plan) for a new product to be submitted during the course of such a program.

EFPIA CAUTIOUSLY OPTIMISTIC

European pharmaceutical industry group EFPIA is cautiously optimistic about the new approach.

It told the *Pink Sheet* that while it welcomed the authorities' "openness to consider alternative clinical trial designs that address the specificities of small trial populations," it had concerns. "A multi-product, multi-company development programme raises certain regulatory/legal questions," it explained.

As well as the issue of governance and funding of a study, EFPIA said that questions are likely to include, but are not limited to, eligibility for and timing of pediatric reward/incentives, and the potential for a PIP (EU pediatric investigation plan) for a new product to be submitted during the course of such a program.

"Together with individual product characteristics (including route of administration), these must be taken into account in determining on a case-by-case basis whether a multi-arm, multi-company trial may be the optimal approach for a new compound," it said.

Another important question EFPIA says needs to be considered is: when adopting a multi-product, multi-company study, would the PIP applicant be expected to develop additional clinical studies in pediatric patients depending on the specific medicinal product/mechanism of action, or would the EMA's Paediatric Committee not require/waive additional studies?

"A multi-product, multi-company development programme may indeed take away some of the constraints around multiple studies competing for the same pool of eligible paediatric patients," EFPIA commented. "Nevertheless, such a programme per se does not address most areas of unmet medical need."

While questions remain, the trade group said it "welcomes the fact that platform, basket and other types of new, more collaborative trial types and designs continue to be investigated for all ranges of disease." These will be considered in new, large-scale pilots within the framework of the EU's public-private partnership, the Innovative Medicines Initiative, with the support of global heads of R&D, EFPIA said.

"This is also in line with the recently revised ICH [International Council for Harmonisation] E11 guideline which, in its addendum, promotes the use of innovative study design, which can be supported by regulators provided justified, appropriately conducted, and agreed beforehand with those regulators."

STRATEGIC COLLABORATION ON GAUCHER DISEASE

As for the newly published strategic collaborative approach, the EMA and FDA discuss possible ways to enhance the efficiency of medicine development in Gaucher disease, a rare lysosomal storage disorder.

Gaucher disease is being used as a disease model, the document notes, clarifying that the principles in the document may be extended to other areas of drug development in rare diseases. In addition, different approaches may be proposed and the applicant should justify the specific choice of each new strategy, the document states.

"Due to differences in the regulatory requirements of both Europe and the United States, particularly regarding extrapolation of efficacy from adults to children, additional trials may be required to support an application for approval," it adds.

The document deals with general considerations for study population, and practicalities in the design and execution of pediatric trials of drugs for Gaucher disease, and covers the use of extrapolation of efficacy data for the disease.

It also proposes a multi-arm, multi-company trial for non-neurological manifestations of Gaucher disease. This proposal covers issues such as study design features; study population and subset definition; number of study participants by pediatric subset (e.g., age, sex, severity or stage); main inclusion criteria; main exclusion criteria; study duration for participants; dosage, treatment regimen, and route of administration; controls; endpoints with times of assessment; statistical plan (SAP) including study conduct and analysis; measures to minimize pain and distress; and external independent data safety monitoring boards.

The trade group "welcomes the fact that platform, basket and other types of new, more collaborative trial types and designs continue to be investigated for all ranges of disease."

From the editors of Scrip Regulatory Affairs. Published online July 4, 2017

This article was updated on July 5, 2017.

EMA Says Yes To First Sickle Cell Drug For PRIME

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The European Medicines Agency has accepted the first investigational drug for treating sickle cell disease (SCD) onto its priority medicines (PRIME) program for getting products for unmet medical needs to patients faster.

GBT440 is being develop by Global Blood Therapeutics, which has met PRIME's rigorous entry criteria and will now receive early and proactive support from the EMA to help optimize its development plan. PRIME also offers the chance of an accelerated assessment.

SCD represents a global health problem for which "new treatment options are desperately needed," the company said. The only EU-approved medication for treating SCD is hydroxyurea, which was authorized as Siklos in 2007. However not all patients respond to hydroxyurea.

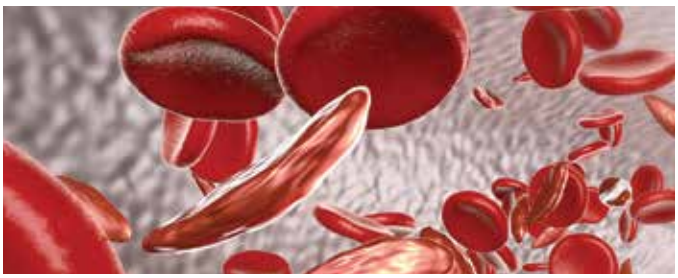
Data from the Pharmaprojects database shows that piracetam is registered for the treatment of sickle cell anemia in certain countries – Armenia, Azerbaijan, Belgium, the Czech Republic, Georgia, Hungary, Kazakhstan, Luxembourg, Myanmar, Moldova, Singapore, Slovakia, Thailand, Ukraine and Uzbekistan.

Access to the PRIME program "provides further recognition from a regulatory authority that SCD is a severely unmet medical need that requires attention," said GBT president and CEO Ted Love. It also provides "external validation of the potential of GBT440 to address this need and bring a major therapeutic advantage to patients." GBT440 has been granted orphan status in both the EU and US. The US Food and Drug Administration has also granted it fast-track designation.

GBT440 was one of two investigational products to get accepted onto PRIME in June, the EMA revealed earlier this week. Roche's polatuzumab vedotin was also accepted, for treating people with relapsed or refractory diffuse large B cell lymphoma (DLBCL), the most common aggressive form of non-Hodgkin lymphoma. There are currently 27 products on the PRIME scheme, which was launched in March 2016.

To be accepted for PRIME, a therapy must demonstrate the potential to benefit patients with unmet medical needs through early clinical data. The GBT440 acceptance was supported by data from the ongoing Phase I/II clinical trial (GBT440-001) evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of GBT440 in both healthy subjects and adults with SCD, GTB said. "Additionally, results from this trial, coupled with the well understood molecular pathophysiology of SCD and the mechanism of action of GBT440, support the scientific rationale that improvement in hemolysis and hemoglobin may be likely to translate into an improvement in patient symptoms and important disease modification."

GBT440 is being developed as an oral, once-daily therapy for patients with SCD. It works by increasing hemoglobin's affinity for oxygen. Since oxygenated sickle hemoglobin does not polymerize, GBT believes that GBT440 blocks polymerization and the resultant sickling of red blood cells. With the potential to restore normal hemoglobin function and improve oxygen delivery, the company believes that GBT440 may potentially modify the course of SCD.



Access to the PRIME program provides "external validation of the potential of GBT440 to address" SCD – GBT president and CEO Ted Love

GTB is one of a number of companies developing drugs for sickle cell disease. Other developers include Bluebird bio (*LentiGlobin*), Emmaus Life Sciences (L-glutamine), Pfizer (rivipansel), Novartis (SEG101/crizanlizumab)), Sancilio Pharmaceuticals (SC411), and EDE Pharmaceuticals (Pedroxa).

A FIRST FOR ROCHE

As for Roche's PRIME designation, the company said it was the first time it had been accepted onto the scheme. Polatuzumab vedotin is an anti-CD79b antibody drug conjugate consisting of an anti-CD79b monoclonal antibody that is linked to a potent microtubule-disrupting agent.

The PRIME designation is for the use of polatuzumab vedotin in combination with MabThera (rituximab) and bendamustine for treating relapsed or refractory DLBCL. It was primarily based on results from a randomized Phase II component of Roche's GO29365 study in people with relapsed or refractory DLBCL that compared treatment with polatuzumab vedotin plus bendamustine and MabThera/Rituxan with bendamustine plus MabThera/Rituxan.

The PRIME designations for BTG and Roche were adopted by the EMA's Committee for Medicinal Products for Human Use at its meeting on June 19-22. The committee reviewed 10 applications for PRIME in total and rejected eight. The rejected applications covered drugs for treating diabetic gastroparesis, acute myeloid leukaemia, autism spectrum disorder, myasthenia gravis, soft tissue sarcoma, mesothelioma, HIV infection, and partial deep dermal and full thickness burns.

From the editors of Scrip Regulatory Affairs. Published online June 30, 2017

US BIOSIMILARS: 40% First-Cycle Approval Rate Leaves Room For Improvement

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Five years into the legislation that created FDA's biosimilar user fee system, a 40% first-cycle approval rate for publicly disclosed applications leaves ample room for progress under the program's next iteration.

While FDA has consistently met its Biosimilar User Fee Act (BsUFA) performance goals for reviewing and acting on a set percentage of original 351(k) application submissions within 10 months, those actions, for the most part, have not been approvals.

Four of the first 10 publicly disclosed biosimilar applications were approved on the first review cycle, while six received complete response letters. There has been one second-cycle approval, **Celltrion Inc.**'s *Inflectra* (infliximab-dyyb), and one publicly disclosed second-cycle complete response letter, for **Hospira Inc.**'s (**Pfizer Inc.**) erythropoietin *Retacrit*.

The first-cycle approval rate, as well as FDA's struggles to hold timely meetings with sponsors, under the inaugural program reflect the targeted objectives for the BsUFA II agreement negotiated by FDA and industry. While the agency wants to see an improvement in the quality and completeness of 351(k) applications submitted for review, industry wants more timely and complete advice from the agency on development programs and agency expectations.

However, a key Republican lawmaker has already said that the number of biosimilar approvals, and the rate of first-cycle approvals, will be key to gauging FDA's performance over the next five years under BsUFA II. *(Also see "Biosimilars: Next User Fee Cycle Will Be Judged On US FDA's Approvals, Rep. Burgess Says" - Pink Sheet, 15 Mar, 2017.)*

15 DISCLOSED SUBMISSIONS = 5 APPROVALS ...

The FDA Safety and Innovation Act (FDASIA), signed into law July 9, 2012, established the biosimilar user fee program that took effect on Oct. 1, 2012.

While FDA has consistently met its BsUFA performance goals for reviewing and acting on original 351(k) submissions within 10 months, those actions, for the most part, have not been approvals.

Through July 5, 2017, sponsors have publicly disclosed the filing of 15 biosimilar applications. Of these, five have been approved, although only two – **Sandoz Inc.**'s *Zarxio* (filgrastim-sndz) and **Amgen Inc.**'s *Amjevita* (adalimumab-atto) – were licensed within the standard 10-month review period on the first review cycle.

Two of the five licensed biosimilars – Sandoz's *Erelzi* (etanercept-szzs) and **Samsung Bioepis Co. Ltd.**'s *Renflexis* (infliximab-abda) – required three-month user fee extensions during the first review cycle, while the other licensed biosimilar, Celltrion's Inflectra, was approved in the second cycle.

... 5 CRL'ED APPLICATIONS ...

Another five applications have been held up by complete response letters, with three of these coming on applications referencing Amgen's *Neulasta* (pegfilgrastim), a pegylated leukocyte growth factor which is proving to be a tough biologic to copy, at least to FDA's satisfaction. *(Also see "Taking Biosimilars Down A PEG: Why Copying Neulasta Isn't So Easy" - Pink Sheet, 13 Jun, 2017.)*

Following its receipt of a complete response letter in June, **Coherus BioSciences Inc.** suggested its proposed Neulasta biosimilar would be delayed at least a year. Sandoz, meanwhile, is conducting a new study on its pegfilgrastim product to satisfy FDA's July 2016 complete response letter; the application is targeted for resubmission in 2018.

Apotex Inc., a privately held company, has not confirmed receipt of complete response letters for its proposed biosimilars to Neulasta or Amgen's *Neupogen* (filgrastim). However, both applications had user fee goal dates in 2015, and FDA's BsUFA performance reports for the applicable fiscal years indicate the agency took timely action on the applications – actions presumed to be complete responses.

Hospira's Retacrit, a proposed biosimilar of Amgen's *Epogen* (epoetin alfa), has the ignominious distinction of drawing two complete response letters, the second of which came in June and resulted from lingering compliance issues at a Kansas manufacturing facility. *(Also see "Pfizer's EPO Biosimilar Stalls In US On Hospira Compliance Woes" - Pink Sheet, 22 Jun, 2017.)*

... AND 5 PENDING

FDA is currently reviewing the remaining five publicly disclosed applications, with goal dates that range from September 2017 to February 2018.

Two of the pending applications –

Mylan NV's and **Biocon Ltd.** MYL-1014O, a proposed biosimilar to **Genentech Inc.**'s *Herceptin* (trastuzumab), and **Amgen Inc.** and **Allergan PLC**'s ABP 215, which references Genentech's *Avastin* (bevacizumab) – head to an FDA advisory panel review on July 13. Although the Oncologic Drugs Advisory Committee previously reviewed the applications for Zarxio and Retacrit, the upcoming panel meeting will mark the first for biosimilars of anticancer drugs, as opposed to supportive care agents used in the oncology setting.

Thus far, FDA has stuck to its publicly stated plans to take the first biosimilar application for a given reference product to a panel review, at least in the BsUFA program's early years.

However, the agency also has said it will only take to panel review those first-in-class applications for which the analytical data support a finding of high similarity to the reference product. This explains why advisory committee meetings, thus far, have not been convened for applications that end up with first-cycle complete response letters. The Retacrit meeting occurred during the second review cycle, seemingly after substantive issues raised during the application's first-cycle review had been addressed by Pfizer.

The agency also has shown that it is willing to skip a panel review for subsequent biosimilars to the same product. Samsung's Renflexis, the second biosimilar to **Janssen Biotech Inc.**'s *Remicade* (infliximab), was the first 351(k) application to win approval without an advisory committee stopover.

Similarly, no meeting has been announced for **Boehringer Ingelheim GMBH**'s BI 695501, which is in line to become the second biosimilar to **AbbVie Inc.**'s *Humira* (adalimumab), following in the footsteps of Amgen's Amjevita,

HIDDEN APPLICATIONS?

FDA may have more on its biosimilar application review plate than meets the eye.

The agency's FY 2016 BsUFA Performance Report states that it received five original biosimilar product applications from Oct. 1, 2015 to Sept. 30, 2016. *(See table, p. 8)* However, only three of those applications appear to have been publicly disclosed: Amgen's Amjevita, Samsung's Renflexis and Coherus' CHS-1701.

FDA said the BsUFA report provides the preliminary numbers for FY 2016 and reflects data as of Sept. 30, 2016.

"The number indicated of five on the original biosimilar product applications submitted in FY 2016 includes those applications that have been filed, and those applications that are currently within the 60-day filing period and have not yet reached their filing date," FDA said in response to questions from the Pink Sheet. "It does not include applications that were refused-to-file, withdrawn before filing, or unacceptable for filing due to nonpayment of user fees."

For years, FDA officials have made clear that their public remarks about the number of biosimilar applications refer only to those submissions publicly disclosed by sponsors.

"Companies can elect to voluntarily disclose their application status to the public and this could vary from the numbers that FDA reports depending on the status of their application at any given time," the agency said of the number of submissions reported in the FY 2016 performance report.

It's possible that the two undisclosed applications submitted in FY 2016 were the subject of an FDA refuse-to-file action or voluntary withdrawal by the sponsor after Sept. 30. However, if the applications were filed by the agency their user fee dates would be coming due. For example, an application submitted at the end of September 2016 would have a 10-month review goal date in late July.

It's possible that an application submitted near the end of FY 2016 could have received a refuse to file letter and been resubmitted in FY 2017. To date, five applications have been publicly disclosed as having been submitted during the current fiscal year.

Amgen said its November submission for ABP 215 was its first for that product. Similarly, Mylan's 351(k) applications for MYL-1401H and MYL-1401O, referencing Neulasta and Herceptin, respectively, are the original applications, the company said.

Celltrion said the BLA for CT-P10, a proposed biosimilar to Genentech's *Rituxan* (rituximab) that was accepted for filing in June, was company's first submission for the product.

Boehringer Ingelheim declined to comment as to whether the November submission for its proposed Humira biosimilar was the original application for the product.

Coherus said its August 2016 submission for CHS-1701 was the first application for that product.

Apotex, which has publicly disclosed only the 2014 submissions for proposed biosimilars to Neulasta and Neupogen, said it has not submitted any 351(k) applications that FDA has either declined to review or the company has voluntarily withdrawn.

Sandoz, which holds two of the first five approved biosimilar applications, declined to say whether it has submitted any 351(k) applications that FDA either refused to file or the company voluntarily withdrew.

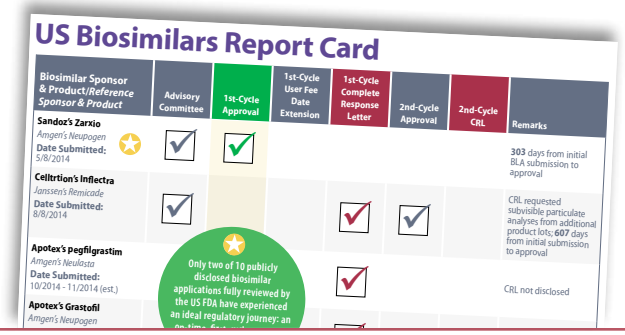
Neither Pfizer nor Hospira has voluntarily withdrawn a 351(k) application or had FDA refuse to accept an application, Pfizer said.

Samsung declined to comment on whether it has submitted any biosimilar applications that were turned away or voluntarily withdrawn.

FDA said it could not provide data on the numbers of complete response letters, refuse-to-file actions, applications voluntarily withdrawn before filing, or applications deemed unacceptable for filing due

CLICK

For a report card on individual products' progress through key FDA review milestones, visit our website at http://bit.ly/2uyrZeT



Original Biosimilar Product Applications: Review Goals And Performance

ORIGINAL BIOSIMILAR APPLICATIONS	FY 2015	FY 2016 (PRELIMINARY)
Total Submissions	**5**	**5**
Pending	0	4
On-Time	5	1
Overdue	0	0
Performance % On-Time	100%	100%
BsUFA Goal: On-Time Target %	80%	85%
Goal Met Status	Met	Currently meeting, pending

Source: FY 2016 BsUFA Performance Report (data as of Sept. 30, 2016)

to nonpayment fees under BsUFA.

Such metrics "represent data associated with unapproved applications," FDA said, adding that it cannot discuss products in development.

FIRST-CYCLE APPROVAL RATE COMPARABLE TO PDUFA I

Despite stakeholder dissatisfaction with the number of first-cycle approvals for publicly disclosed biosimilars, the rate is comparable to that seen in the early years of the Prescription Drug User Fee Act (PDUFA) program and well ahead of its brethren generic drug program.

PDUFA I ran from FY 1993-1997. Of the novel applications submitted in FY 1996, 44% were approved in the first cycle, and that number reached more than 50% for the FY 1997 cohort, according to agency performance reports.

PDUFA is now in its fifth iteration; FDA's FY 2016 PDUFA Performance Report shows that 65% of standard applications and 85% of priority applications submitted in FY 2015 received a first-cycle approval.

Like BsUFA, the Generic Drug User Fee Act (GDUFA) program also was established in FDASIA. The first-cycle approval or tentative approval rate for original abbreviated new drug applications (ANDAs) submitted in the third year (beginning October 2014) of GDUFA I was 8%, with 43% receiving a second-cycle approval or tentative approval, according to preliminary data as of Sept. 30, 2016. *(Also see "Generic Drug First-Cycle Approval Rates Lagging Under GDUFA I" - Pink Sheet, 25 Oct, 2016.)*

Despite the relatively favorable comparisons for BSUFA I relative to PDUFA I and GDUFA I, the high price of biologics and the potential for significant cost-savings with biosimilars, particularly when multiple versions of the same reference product enter the market, mean there will continue to be high external expectations for FDA to approve more 351(k) applications more quickly.

PRE-SUBMISSION MEETINGS COULD HELP TURN THE TIDE ...

The agency is hopeful that changes negotiated with industry in the BsUFA II agreement will improve the quality of biosimilar applications that come through the door and boost the first-cycle approval rate.

A key feature of BsUFA II, which is making its way through the House and Senate as part of comprehensive user fee legislation, is the addition of two months to the review period in exchange for increased communications and interactions between FDA and sponsors before and during the review process. *(Also see "Biosimilars Will Get PDUFA-Style Reviews Under New User Fee Plan" - Pink Sheet, 28 Sep, 2016.)* This review model, known as The Program, was implemented in PDUFA V for new molecular entities and novel biologics.

"The goal of The Program is to improve the efficiency and effectiveness of the first-cycle review process by increasing communication during application review," FDA said in a recent Federal Register notice on the biosimilar program. "This will provide sponsors with the opportunity to clarify previous submissions and provide additional data and analyses that are readily available, potentially avoiding the need for an additional review cycle when concerns can be promptly resolved without compromising FDA's standards for approval."

At the Drug Information Association's annual meeting in June, Leah Christl, associate director for therapeutic biologics in FDA's Center for Drug Evaluation and Research,

FDA reported receiving five original biosimilar product applications between Oct. 1, 2015 to Sept. 30, 2016, although only three of those submissions appear to have been publicly disclosed by sponsors.

highlighted the importance of the BsUFA II review program's pre-submission meeting between the agency and sponsor to discuss the planned content of an application and reach agreement on which application components can be submitted late. *(Also see "Best Of Biosimilar Agreement: FDA, Industry Tout Written Response, Pre-Submission Meeting" - Pink Sheet, 29 Jun, 2017.)*

"We are hoping sponsors have pre-application meetings and not just submit an application to FDA and hope for the best," Christl said. "That will be a change for both industry and FDA on how we approach application review."

... AS COULD MORE TIMELY FDA ADVICE

The BsUFA II agreement also includes measures aimed at addressing FDA's continuing struggle to meet some of its meeting management performance goals under BsUFA. *(Also see "FDA Met Biosimilar Review Timelines But Missed Meeting Goals In 2015" - Pink Sheet, 25 Apr, 2016.)*

The preliminary FY 2016 data show the agency continues to fall short of its performance goals for scheduling four out of five types of meetings under BsUFA and in providing meeting minutes to sponsors.

From a scheduling perspective, the most problematic are Biosimilar Biological Product Development (BPD) Type 2 meetings. These meetings – which are held to address a specific issue, such as study design or endpoints, or other questions where FDA will provide targeted advice – represent the largest single category of meetings in the BPD program.

In FY 2015, only 49% (20 of 41) of Type 2 meetings were scheduled within 75 days, falling well short of the 80% performance goal, according to the final data for the year. The situation in the preliminary FY 2016 data appears far improved but is still shy of the 85% performance goal for the fiscal year – as of Sept. 30, 2016, 73% of Type 2 meetings were scheduled on time, with a highest possible performance of 74%.

The BsUFA II agreement allows sponsors to request a written response to questions rather than a face-to-face meeting or teleconference in the BPD Type 2 category, which could provide more efficiencies for sponsors and FDA alike. In addition, the scheduling timeframe for such meetings is increased from 75 to 90 days, giving agency staff more breathing room.

Published online July 6, 2017

FDA's NDA And BLA Approvals: Triptodur, Pantoprazole, Omeprazole

Below are FDA's original approvals of NDAs and BLAs issued in the past week. Please see key below chart for a guide to frequently used abbreviations

SPONSOR	PRODUCT	INDICATION	CODE	APPROVAL DATE
New Drugs				
Arbor	*Triptodur* (triptorelin)	Extended-release injectable suspension formulation of the gonadotropin-releasing hormone agonist for treatment of pediatric patients age two years and older with central precocious puberty.	S, 5	6/29/2017
Hetero	Efavirenz/ lamivudine/ tenofovir disoproxil fumarate	Combination of Sustive 600 mg/Epivir 300 mg and Viread 300 mg to be used alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 40 kg. (Tentative approval.)	P, 4	6/30/2017
Exela	Pantoprazole sodium	40 mg/vial for injection for short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis and treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome in adults.	S, 5	6/30/2017
Dexcel	Omeprazole	20 mg, orally disintegrating, extended-release tablet of the proton pump inhibitor	S, 8	7/5/2017

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

Code Cart Crisis: Anatomy Of An Emergency Drug Shortage

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New shortages of emergency drugs from the overstressed US sterile injectables manufacturing sector are posing difficult challenges for US health care providers.

Syringes typically are prefilled with these injectable drug products and stocked in hospital code carts' top drawers for immediate access in case of cardiac arrest.

Some treat other life-threatening conditions like insulin shock, severe allergic reactions and insecticide poisoning.

Pharmaceutical companies are responding with the type of heroics you might expect to see in emergency rooms rather than in manufacturing plants.

But much like some heart attack victims, those companies have been running their aging, sclerotic manufacturing lines with very little downtime, deferring maintenance, putting off upgrades, hoping something doesn't come along and flat line the whole operation.

The code cart crisis underscores a broader failure in the US market: few companies are willing to invest in making older drug products that are central to the practice of medicine. The companies that still make them do it with manufacturing processes and supply chains that are increasingly fragile. *(Also see "High Utilization Seen as GMP Issue Behind Cancer Drug Shortages" - Pink Sheet, 25 May, 2012.)*

A SERIES OF SHORTAGES

In recent years, quality shortfalls related to these challenges have triggered a series of shortages of critical injectable drugs manufactured domestically for the US market.

Shortages of methotrexate and other injectable cancer drugs including **Janssen Products LP**'s Doxil followed efforts by **Boehringer Ingelheim Corp.** to remediate its **Ben Venue Laboratories Inc.** unit's Bedford, Ohio, plant. The company suspended operations in November 2011 to fix an array of quality problems, and in October 2013 decided to close the plant rather than go beyond the $350m it had by then sunk into remediation. *(Also see "US cancer drugs shortage crisis drives temporary drug importation, quick approval and draft guidance " - Pink Sheet, 23 Feb, 2012.)*

Fearing shortages, healthcare providers began hoarding saline solution in the months after a May 2013 FDA warning letter focused on microbiological contamination at **Baxter Healthcare Corp.**'s facility in Marion, NC, and on leaky bags of injectable drugs at its Jayuya, Puerto Rico, plant. Shortages soon followed, although Baxter attributed them to the increase in demand, which outpaced its increase in production, rather than to concerns about quality. *(Also see "Shortage Within A Shortage: Baxter Adjusts Allocation Of I.V. Products As Shortage Drives Demand" - Pink Sheet, 26 Mar, 2014.)* The quality issues at the Marion plant were the subject of an $18m consent decree filed earlier this year. *(Also see "The Case of Baxter's Moldy HEPA Filters" - Pink Sheet, 26 Jan, 2017.)*

Luitpold Pharmaceuticals Inc. triggered a shortage of total parenteral nutrition products when it suspended operations in late 2012 at its in Shirley, NY, manufacturing facility to resolve problems with particulates in vials of TPN electrolytes such as sodium phosphates injection USP and calcium gluconate injection USP. This shortage drew attention from Congress as members heard an outcry from parents of premature infants who required TPN for survival. *(Also see "As Drug Shortages Linger, Attention Turns to TPN Crisis" - Pink Sheet, 30 May, 2013.)*

> Pfizer says it has made it a priority to manufacture the medically necessary products and has "a dedicated team focused on working to address the shortages and expedite supply recovery."

A LACK OF COMPETITION

As with other drug shortages, today's code cart crisis resulted in part from a lack of competitors to take up the slack when problems arose.

Pfizer Inc. says manufacturing, distribution and third-party delays at the **Hospira Inc.** sterile injectables unit it acquired in September 2015 are behind the shortages of five injectable drugs the company announced June 16 – sodium bicarbonate, dextrose 50%, epinephrine, calcium chloride and atropine sulfate.

For many of these products, only one manufacturer is listed in FDA's drug shortage database as an alternative source – **Amphastar Pharmaceuticals Inc.**'s International Medication Systems Ltd. (IMS) sterile injectables unit in South El Monte, Calif.

Luitpold Pharmaceuticals Inc. also makes certain presentations of some of these drugs, and **West-Ward Pharmaceuticals Corp.** makes one.

FDA is looking into what it can do to stir up more competition to produce such lifesaving but often scarce drug products.

A RECALL ADDS TO CRISIS

One of the emergency medicines now in shortage, sodium bicarbonate, became scarcer still after additional quality concerns triggered a recall.

Pfizer told health care providers the sodium bicarbonate shortage began when its Rocky Mount, NC, plant had difficulty obtaining certain components of prefilled glass syringes. This led to the syringe shortage, which in turn precipitated a vial shortage. Then came a media fill failure.

After detecting microbial growth during a routine simulation of the manufacturing process, Pfizer's Hospira unit recalled 42 lots of 8.4% sodium bicarbonate injection 50 ml vials.

Hospira said no adverse events have been reported, nor have microorganisms been found in any of the affected batches. But the media fill failure meant it couldn't assure the sterility of a substantial amount of product. Hospira said it has begun an investigation to identify the root cause as well as corrective and preventive actions.

"The sodium bicarbonate shortage is particularly grim," Erin Fox, senior director, Drug Information Service, University of Utah Health Care, told the Pink Sheet by email. "I can tell you that at our system we just lost half our stock."

HOW HEALTH SYSTEMS ARE RESPONDING

The American Society of Health-System Pharmacists (ASHP) advises members on how to conserve supplies of shortage drugs while managing the safety risks associated with alternative approaches. The willingness of ASHP members to incur those risks is a testament to the gravity of today's drug shortage problem.

During the sodium bicarbonate shortage, for example, ASHP says sodium acetate, also in short supply, can serve as an alternative, at least for some indications, although it can take 10 times longer to infuse.

Providers can draw up doses from vials, if available, instead of the hard-to-find syringes, but should take care to ensure sterility as per US Pharmacopeia General Chapter <797>. And in any case, many of the vials have been recalled due to sterility concerns.

ASHP says sodium bicarbonate injection is commonly used in critical care settings during advanced cardiac life support. It's also used in managing metabolic acidosis and hyperkalemia, and as an antidote for tricyclic antidepressants, methyl alcohol, phenobarbital and salicylates.

ASHP suggests alternatives for certain non-emergency uses including relying on oral sodium bicarbonate tablets or dissolving baking soda into water. The Society of Critical Care Medicine has additional recommendations to help preserve prefilled sodium bicarbonate syringes for emergency use.

THE RISKS OF EPINEPHRINE OPTIONS

ASHP and the Institute for Safe Medication Practices warn against several measures health systems might take to conserve the prefilled 1 mg/10 ml epinephrine syringes that ride on code carts and emergency vehicles.

Any attempts to substitute with the 1 mg/10 ml emergency syringes that come with intracardiac needles can injure both the patient and the caregiver.

Nor is bulk compounding an option because extemporaneously prepared epinephrine has poor stability due to sensitivity to light, air and pH.

The 30 ml multiple-dose vials should not go in code carts, because they facilitate accidental overdoses.

If practitioners use 1mg/ml ampoules or vials in an emergency, they might miscalculate doses. ISMP has reported cases where patients died because of such miscalculations.

The institute says the risk of confusion is exacerbated by the type of labeling the US Pharmacopeia allows for epinephrine, which FDA does not regulate since the unapproved drug is grandfathered under the Food, Drug & Cosmetic Act.

If such ampoules or vials are to be used in place of emergency syringes, ISMP says to put them in plastic bags labeled with drug name and strength, along with instructions for properly diluting them in 9 ml of sodium chloride 0.9%.

MORE STEPS FDA AND PFIZER ARE TAKING

FDA says it's working with Pfizer on a variety of measures to relieve the shortages and address underlying causes.

The agency has agreed to extend the use dates of certain lots of emergency syringes six months beyond the original expiry dates, nine months for epinephrine, based on stability data Pfizer provided.

The extensions apply so far to 57 lots of sodium bicarbonate injection, 80 lots of dextrose 50% injection, 110 lots of epinephrine injection and 40 lots of atropine sulfate injection.

FDA is not requiring Pfizer to relabel the lots with the new use dates, and expects providers to replace and dispose of expired lots as soon as possible, even if they're still considered usable.

Pfizer told the Pink Sheet it also has made it a priority to manufacture the medically necessary products, saying it has "a dedicated team focused on working to address the shortages and expedite supply recovery."

The company told customers in a May 16 letter signed by two marketing officials that it has the taken the additional steps of "increasing production at key injectables manufacturing plants, and qualifying alternative third-party suppliers who meet Pfizer quality standards, as well as increasing inventory levels for 'key manufacturing materials.'"

AUSTRALIA DELIVERS LIMITED RELIEF

Meanwhile, FDA has cleared an Australian firm to export sodium bicarbonate vials to the US.

Athenex Pharmaceutical Division LLC (**Athenex Inc.**) Buffalo, NY, said May 31 that in coordination with FDA, it began temporarily importing 10 ml and 100 ml single-use vials of 8.4% sodium bicarbonate injection from Phebra Pty Ltd., which manufactures and markets it in Australia.

A May 23 letter to health care providers explains that, among other things, Phebra's barcode may not register accurately on US scanning systems. Providers must manually input the product into

their systems and follow alternative procedures to make sure it's given to the right patients.

University of Utah's Erin Fox said that in any case, only small amounts of the Australian product are available.

Fox noted that it is possible to order sodium bicarbonate injection from outsourcing pharmacies regulated under Section 503B of the FD&C Act, but that it would take them four weeks to fill new orders.

WHY UPGRADES MUST WAIT

It's no secret that facilities like Pfizer's Rocky Mount plant are in need of upgrades.

Over the past few years, workers there have been complaining anonymously at the Glassdoor jobs and recruiting website about outdated manufacturing lines and equipment that is always breaking down.

A Hospira engineering VP told an April 2015 workshop on aging facilities why the company has been loath to invest in major plant upgrades there. *(Also see "A Day of Reckoning for Aging Facilities: Is It Time to Invest in Change?" - Pink Sheet, 25 Sep, 2015.)*

While cost is an issue, the bigger hurdle is time.

If you're a sole supplier of a product on drug shortage, Hospira's Craig Johnson explained, "at the end of the day, you're probably running your manufacturing operation at 100% utilization just to keep up with demand or just to try to keep the product off the drug shortage list. So guess what? That makes very little time for an engineering guy to come in and say, 'I've got $20 million approved. Let's go and take this line out of service for six months and do this great modernization project.'"

From the editors of the Gold Sheet. Published online July 6, 2017

REGULATORY UPDATE

Despite Brexit, UK Regulator Remains Pharma Favorite – For Now

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The uncertainty caused by Brexit has prompted EU regulators – at both European Medicines Agency and national agency level – to issue a long list of changes that drug companies should consider to keep their establishments on the right side of EU law, but the industry is showing no signs of panic.

On the contrary, since June last year when the UK voted to leave the EU, there has been a "small rise" in the number of new applications under the decentralized procedure (DCP) where companies have chosen the UK to act as the reference member state (RMS).

"So it's not coming down; it's rising… This was unexpected," said Dr Hugo Hurts, the head of the Dutch Medicines Evaluation Board and a member of the management group of the EU Heads of Medicines Agencies grouping.

This rise only applies to new applications for human medicines. With veterinary medicines, "we are now seeing a modest decline" in the number of new DCP applications with the UK as the RMS, Hurts told the *Pink Sheet* in an interview. Though the changes are "not very spectacular," Hurts said that on the veterinary side "things seem to have started moving."

> The UK's MHRA is the reference agency for some 3,400 human medicines evaluated through the decentralized procedure.

The rise in new DCP applications for human medicines with the UK as the RMS is surprising because marketing authorization holders (MAHs) know that if the UK leaves the EU network following Brexit, they will have to reassign the task of the RMS to an agency of a member state in the European Economic Area. *(Also see "Change And More Change: That's What Brexit Means For Drug Companies" - Pink Sheet, 1 Jun, 2017.)*

At present, the UK Medicines and Healthcare products Regulatory Agency (MHRA) is the RMS for some 3,400 human medicines evaluated through the DCP, while the UK's Veterinary Medicines Directorate (VMD) is the RMS for some 600 products. If, as is anticipated, the UK leaves the EU, "the remaining member states in the [EU medicines] network will have to deal with approximately 4,000 changes of reference member states," Hurts said. Brexit is expected to happen at the end of March 2019.

Changes to the RMS can be particularly complex and time-consuming because the MAH has to ensure that there is agreement with both the current and future

RMS, and that no pending procedures are outstanding. To change the RMS, the MAH would have to ensure that its application is "clean… without any open variations," Hurts said.

However, so far "we see no clear signs from the side of pharmaceutical companies" that they are moving away from having the UK as the RMS in their DCP applications, Hurts added. He pointed out that it is up to companies to take the initiative on this "because they are ultimately responsible for having a reference member state that is [located] in the EU. So they have also to decide on when to make the shift."

Hurts believes that pharmaceutical companies have "a lot of thinking" to do before they are in a position to start changing the RMS. "To be honest, our impression is that pharmaceutical companies at the moment are still experiencing uncertainties connected to the rollout of the Brexit procedure… More time and clarity [is] needed before we see large shifts of reference member states," he added.

PLANNING FOR WORST, HOPING FOR BEST

EU regulators are not waiting for a final decision on the terms of the UK's departure from the union. They have already begun planning for the worst-case scenario where the UK would have the status of a third country and the MHRA would no longer be part of the network. Nonetheless, "we all hope that it won't get as bad as that," said Prof. Klaus Cichutek, president of Germany's Paul Ehrlich Institute and chair of the HMA's management group.

EMA BREXIT WORKSHOP WITHOUT UK REGULATORS

Hurts said that EU regulators started discussing the implications of Brexit "very early on," but the UK government's formal triggering of the so-called Article 50 in late March prompted the European Medicines Agency to organize a dedicated Brexit workshop in April without British regulators. "It was possibly the first time that we were in the EMA office without the presence of the British [delegation] there… [The aim was to] bring together the necessary data, primarily on centralized procedures under EMA responsibility," Hurts recalled.

> "This was possibly the first time that we were in the EMA office without the presence of the British" – Hugo Hurts, head of Dutch Medicines Evaluation Board

Following the workshop, the EMA management board set up two working groups – for human and veterinary drugs – to explore options for a robust relocation of the MHRA's and VMD's workload across the network, to streamline the existing work, and to further increase the network's capacity. At the HMA, a separate Brexit task force is analyzing the situation concerning decentralized procedures. The HMA's Brexit task force will work in close collaboration with the EU Coordination Groups for Mutual Recognition and Decentralised Procedures – human and veterinary (CMDh and CMDv) and with the EMA to ensure there is as much oversight and coordination as possible.

Meanwhile, some EU member states are already planning to hire more staff in anticipation of the additional workload coming their way. *(Also see "EU National Agencies Prepare For 'Rebalancing' Of Network Post Brexit" - Pink Sheet, 4 Apr, 2017.)*

Hurts said that the EMA had recently distributed a questionnaire to all EU national competent authorities to get an overview of their plans in this respect. "Around five or six weeks ago, there were messages that a number of NCAs already have concrete plans to expand capacity, but it was not clear at that time who had already started [hiring] and who was still planning, and how all this was going to be financed," Hurts added. This task is not straightforward for NCAs because "it involves carrying out hiring assessment, it needs finances, it needs educating and training new experts on [implementing] regulations."

Hurts confirmed that no "Brexit budget" is being provided by the European Commission, which means that NCAs will have to find their own ways to finance the hiring of extra staff. "So those [NCAs] that would like to do more would have to talk to their government or to whoever provides their budget nationally," Cichutek noted.

Once the UK leaves the EU, Hurts explained, the total amount of work in the network will probably remain the same as it is at the moment. "Only the distribution is going to be different. So it is a difficult calculation for everyone because no one is certain at the moment what will come its way. The final outcomes of the Brexit negotiations, that still have to start, may also change the situation. So we will need some flexibility obviously," he added.

UK officials, meanwhile, have fully committed themselves to serving the network until the UK leaves the EU. "We have friendly business with each other… [Currently,] there is no finalized plan yet on how or when the UK would hand over its work to the network. In fact, there is really no handover needed because we are all experts in doing the regulatory work that the UK is doing… Whatever handover is needed has to be initiated by the marketing authorization holders," Cichutek said.

On whether the NCAs or the network would extend any financial help to companies that may have to file several variations to ensure their establishments comply with EU law, Cichutek said this required "further planning" and that there were no final plans concerning this. "Much will also depend on the exact nature of the future relationship of the UK with the EU, so we can't give a final answer as yet," he added.

Separately, the CMDh has told companies that "to be not prepared is a risk" and that they should not "expect to be rescued" by agencies if they have not taken the necessary regulatory measures to comply with EU law post Brexit.

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Lobbying Pays Off As UK Ministers Speak Out On Post-Brexit Regulatory Collaboration

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Will the UK biopharmaceutical industry get the kind of post-Brexit UK-EU regulatory cooperation agreement it has been pushing for? Things seem to be shifting in that direction after two senior government ministers publicly stated that the UK was "fully committed to continuing the close working relationship" between the UK and the EU in medicines regulation.

In a July 4 letter to the Financial Times, the health secretary Jeremy Hunt and business secretary Greg Clark said the UK wanted continued cooperation in the interests of public health and safety once the country left the EU.

Close collaboration, they said, had led to more than 130 new products being licensed, and the aim now should be to provide "certainty and long-term stability," with a focus on initiatives to support development of the next generation of products. Noting that drug development was a global business, they said "we will look to continue to work closely with the European Medicines Agency and our international partners."

"Our aim is to ensure that patients in the UK and across the EU continue to be able to access the best and most innovative medicines and be assured that their safety is protected through the strongest regulatory framework and sharing of data," they wrote.

Three principles underlined this approach, they said: patients should not be disadvantaged, innovators should be able to get their products into the UK market as quickly and simply as possible, and "we continue to play a leading role promoting public health."

Fears have been expressed about regulatory divergence and possible delays to new drug launches if the UK opts for a so-called "hard" Brexit, and the industry welcomed the letter as "a significant step forward." Steve Bates, CEO of the UK BioIndustry Association, said: "We are the first sector to get such a public commitment from the new government on a key area."

Bates's counterpart at the Association of the British Pharmaceutical Industry, Mike Thompson, saw the letter as "a welcome recognition that the future of medicines regulation is a key priority for the government as we negotiate a new relationship with the EU."

It was, Thompson said, "a great first step and we look forward to seeing more detail in the coming weeks and months. If patients in Europe are to continue to get safe and effective medicines in a timely fashion, the focus must be on agreeing regulatory partnership between the UK and the EU."

Ministerial words are of course one thing, and actions another, particularly given the continuing uncertainty over the kind of Brexit the government wants to see. And while ministers appear newly emboldened to speak out after the June general election in which prime minister Theresa May's authority was substantially diminished, there is no guarantee that these words will be turned into deeds, or any indication of what form the future arrangements might take.

"We are the first sector to get such a public commitment from the new government on a key area"
– BIA CEO Steve Bates

However, the fact that these two key high-ranking ministers have gone on the record to urge regulatory cooperation amid the Brexit turmoil is significant.

As Bates observed, the decision by the government to publicly communicate its full commitment to continuing the close working relationship with "our European partners' is "good news for patients, industry and investors in the UK and EU. It's the first step to a sensible approach to Brexit for our sector and recognises the negative impact in areas like falsified medicine, pharmacovigilance and infectious disease control that a cliff edge Brexit would cause on both sides of the channel."

Asked whether this special attention was the result of industry lobbying, Bates said: "This announcement shows that government recognises the importance of our sector to the UK's future health and wealth. The life sciences sector was quick to come together in

an organised way following the referendum result and has worked hard for the past year to present a clear and united message to government which they have clearly taken on board."

The ABPI said a "health sector-wide effort" was under way to establish consensus on key Brexit issues such as a regulation, trade, immigration and UK science so as to ensure patients and public health were central to Brexit negotiations. It said "200 global experts" were involved in this effort, including pharmaceutical and biotech companies, academic groups and research charities such as the Wellcome Trust, the MHRA, the NHS and Public Health England, and "a vast range of UK government departments."

The European industry body EFPIA told the *Pink Sheet* recently that industry was pushing for "transitional agreements" that would limit the disruption of Brexit, and that the EU needed to continue to benefit from the current "strong and very successful frameworks." *(Also see "EFPIA Calls For Interim Accords To Ease Brexit Impact" - Pink Sheet, 23 Jun, 2017.)*

BOOSTING THE MHRA

As to what would happen if the UK did not achieve "our desired relationship with the EU," the ministers suggested in their letter that the UK regulator, the Medicines and Healthcare products Regulatory Agency, would be sufficiently resourced to take on the tasks of an independent regulator for the UK, with similar regulatory timelines as at present and with no additional costs for industry.

The government, they said, would "set up a regulatory system that protects the best interests of patients and supports the UK life science industry to go from strength to strength." The MHRA would "seek to process licences as quickly as possible, certainly no more slowly than at present," and "fee pricing will be competitive with current levels." Just where the additional resources to do that would come from remains to be seen.

WHAT KIND OF AGREEMENT?

Any regulatory agreement would presumably aim for some sort of cooperation and mutual recognition system so that the UK could continue to participate in EU drug regulation activities, particularly the centralized (CP), mutual recognition (MRP) and decentralized (DP) procedures.

> "A health sector-wide effort is under way to establish consensus on key Brexit issues such as a regulation, trade, immigration and UK science" – ABPI

The consequence of failure to reach a cooperation and mutual recognition deal would be much broader than applicants needing separate marketing authorizations in both the EU and the UK. Law firm Taylor Wessing notes that there would also be "the unnecessary duplication of certifications and approvals, batch control and release, as well as other measures, for medicines moving between the UK and the EU/EEA, and vice versa under existing MAs."

This, Taylor Wessing says, "is a situation that is likely to be practically, commercially and politically unacceptable to both sides. Most seriously of all, it poses the risk of disrupting the supply of certain medicines to consumers."

"It should be obvious that there is a benefit to both applicants and regulators for the MHRA to remain part of the CP, MRP and DCP, post-Brexit," the law firm said. "The question remains whether or not it is possible to achieve this politically."

Taylor Wessing further notes that the failure of the Conservative government to obtain a majority of MPs in parliament in the general election "has raised speculation that the UK may need to seek a watered-down Brexit in which it remains in the EEA, at least for a transitional period. EEA membership should mean continuation of the UK's participation in the CP, MRP and DCP. However, it is far from clear that this will happen."

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FDA Gives Drug Makers One-Year Reprieve From DSCSA Product Identifier Requirement

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FDA will give pharmaceutical manufacturers an extra year before penalizing them for failing to meet a Nov. 27 Drug Supply Chain Security Act (DSCSA) deadline for starting to affix individual pharmaceutical packages with a unique serial code to allow tracking shipments to US dispensers, the agency said June 30.

This action was prompted by industry complaints on their lack of readiness to meet the legislation's product identifier requirement. The agency said it will delay enforcement until Nov. 26, 2018.

DSCSA mandates that manufacturers and their trading partners track and trace pharmaceutical products through the supply chain, and the law calls for this to be implemented in three waves. The first step, the lot-level tracing requirement, went into effect in 2015. The second step, serialization, requires manufacturers to affix unique identifiers at the individual unit level and the case level. The third step is a package-level electronic, interoperable system, to be established in 2023.

This announcement to delay enforcing the serialization provision was made in a June 30 draft guidance. In it, the agency announced that "FDA does not intend to take action against manufacturers who do not affix or imprint a product identifier to each package and homogeneous case of products intended to be introduced in a transaction into commerce before November 26, 2018. This represents a one-year delay in enforcement of the requirement for manufacturers to affix of imprint product identifiers."

> "One challenge industry cites is the limited number of vendors that have the expertise in data management to help them comply.

This action was in response to comments from manufacturers and trading partners on their lack of readiness in implementing these new serialization requirements. One challenge industry cited is the limited number of vendors that have the expertise in data management to help them comply.

The guidance states that "FDA recognizes that some manufacturers may need additional time beyond November 27, 2017, to ensure that products are properly labeled with a product identifier."

At recent industry meetings, the pharmaceutical industry was warned about the logistical as well as the cost challenges in complying with DSCSA.

At one meeting, an official from **AbbVie Inc.** said industry needs to be well-prepared to ensure that all drug packages are correctly serialized so they are not removed from the supply chain and quarantined. *(Also see "Industry Needs To Be Aware of Serialization Challenges Under DSCSA" - Pink Sheet, 8 May, 2017.)*

At another meeting a pharmaceutical industry official outlined opportunities for pharmaceutical firms to reduce the impact of serialization. *(Also see "Reducing Serialization's Impact On Capital Costs, Equipment Effectiveness" - Pink Sheet, 8 May, 2017.)* It is estimated that package-level serialization for US drug products will cost many companies more than $100m.

The deadline for commenting on the draft guidance is Aug. 28. Comments can be submitted to https://www.regulations.gov, and must reference Docket No. FDA-2017-D-2232.

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OTC Switch Interest Cooled By Study Costs To Update Safety Data

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Pharmaceutical firms get cold feet about potential OTC switches when they consider the costs for studies to update safety data for an ingredient, suggests Laura Mahecha, a health care market consultant for research firm Kline & Co.

During a June 27 webinar, "Key Issues Trending in the US OTC Market," Mahecha noted that with safety "paramount for switch approval," data from a drug ingredient's initial approval for Rx sales might not support allowing OTC sales.

"What we've been hearing in part of our research in the last six months or so, is that many of the switch candidates have been on the prescription market for 10 or more years, so the original safety and efficacy data done to support Rx approval was done over 15 years ago, when measurement tools and technology were very much underdeveloped compared to what we have today," she said.

"So, that's making companies have to either re-analyze old data, or most of the time conduct new safety studies on these medications, and that's proving to be an additional risk factor and cost burden for switch sponsors," added Mahecha, an independent consultant in the consumer product space.

The presentation provided a snapshot into three Kline reports, including "Rx-to-OTC Switch Forecast USA," which forecasts the opportunities and challenges for switches through 2022 and will be available in the fourth quarter.

> For many switch candidates, the original safety and efficacy data for Rx approval was developed "over 15 years ago, when measurement tools and technology were very much underdeveloped compared to what we have today." - Kline's Laura Mahecha

OTC ADDS LAYER TO FDA SAFETY DECISION

FDA encourages switch applications, particularly for ingredients indicated for chronic conditions including high cholesterol, high blood pressure, diabetes and asthma, but Mahecha noted drug firms also are put off by what she called a "higher bar" for approval FDA imposes on OTC switches compared to Rx applications.

Prescription ingredients are tested extensively before new drug applications or abbreviated or supplemental NDAs are submitted; many do not reach FDA when studies show safety or efficacy problems; and they are subjected to lengthy reviews by the Center for Drug Evaluation and Research, often including input from advisory committees, before the agency reaches a decision on approval. Generics and biosimilars of innovative Rx ingredients also go through costly research before applications are submitted and CDER begins its extensive reviews.

OTC switch NDAs have the benefit of following the research and other work conducted for an Rx ingredient's application, but also must convince FDA of an additional safety point. OTC approval requires showing that a product is safe for its indicated use without a health care professional's intervention into a consumer's decision on selecting the product, which entails consumers accurately self-selecting whether they need to use a drug available without prescription and adhering to follow-up directions to determine if they should continue treatment with the product. *(Also see "Pharma Firm ISO OTC Switch Partner; NDA Experience, Resources Needed" - Pink Sheet, 24 Oct, 2016.)*

Concerns about whether consumers will accurately self-select and follow directions when continuing treatment is needed were behind FDA's rejection of three switch proposals by **Merck & Co. Inc.** for a statin ingredient to treat high cholesterol and behind Pfizer Inc.'s decision in 2015 to stop its research to support a switch proposal for a different statin. *(Also see "Light Still On For Switches After Pfizer Pulls Plug On OTC Lipitor" - Pink Sheet, 3 Aug, 2015.)*

For products that are first-in-class for an OTC indication, have a novel mechanism of action or present unique concerns, FDA typically asks an advisory committee to review and recommend whether to approve the application.

Companies may be asked to submit consumer behavior research studies for label comprehension, self-selection and actual use. Although the studies are not always required for a switch, FDA more frequently is asking for consumer behavior research information as meaningful data on whether a drug will be used safely and effectively under OTC labeling. *(Also see "Naloxone Talk Sheds Light On Switch Research Future" - Pink Sheet, 7 Jan, 2013.)*

In addition to safety and efficacy data, including adverse events, for the original prescription drug in switch sponsors' NDAs or AN-

DAs, CDER occasionally will ask for information on OTC use of the ingredient in other countries.

During the webinar, Mahecha identified safety challenges for switch categories analyzed in the Kline report *(see table below)*.

"Our switch research is looking at these categories, but there's specific safety concerns with each one of these, even when they are in existing categories," she said.

For example, in the nasal spray allergy category, companies must tackle the potential for growth suppression in children from systemic absorption of intranasal steroids. In digestive health products, companies face concerns over possible side effects of long-term use off proton pump inhibitors, including risks of bone fracture and renal issues.

The Consumer Healthcare Products Association has said the concern is only relevant to prescription PPIs. *(Also see "Petition Seeks OTC PPI Warning On Cancer Risk From Persistent Heartburn" - Pink Sheet, 2 May, 2017.)*

Firms looking to switch an Rx sleeping aid must study its addiction potential as an OTC, while marketers of topical pain relief candidate drugs must analyze cardiovascular concerns from systemic absorption of topical NSAIDs, Mahecha noted.

Meeting those requirements often comes at a high cost for firms, which weigh the spending against the revenues they estimate from sales of the potential OTC product. A factor in those calculations is whether an OTC switch would launch with three-year market exclusivity, which FDA may allow when clinical trials are part of a switch application. Switches without market exclusivity, or most of them, face generic competition as soon as competing firms receive FDA approval for their products.

Despite those challenges, Kline predicts switches and other factors will help drive growth of the overall OTC market at a compounded annual growth rate of 2.2% and for sales of switched products to grow at a compounded annual growth rate of 5% through 2018.

Switches in 2017 have included **GlaxoSmithKline PLC**'s introduction of *Flonase Sensimist* Allergy Relief (fluticasone furoate) in January, and in February **Sanofi**'s launch of *Xyzal Allergy* (levocetirizine dihydrochloride) in February and Galderma Laboratories L.P.'s debut of *Differin* Gel (adapalene), the first OTC acne ingredient approved in the US in 20 years. *(Also see "Differin Gel Enters Changed Marketplace Since Last OTC Acne Drug Approval" - Pink Sheet, 22 Aug, 2016.)*

WAITING ON NSURE

FDA has acknowledged firms see a barrier to switch and are skeptical of options to ensure safe use of their products, though those options – such as developing extra-label information, instructions or questions that can be accessed online – have been floated by the agency and companies alike. *(Also see "FDA's OTC Naloxone Study Is A Starting Point For Other Switches, Not A Roadmap" - Pink Sheet, 16 May, 2017.)*

FDA began the Nonprescription Drug Safe Use Regulatory Expansion initiative in 2012 to look at potential changes in the application process so sponsors could propose novel switches, including ways to expand safe use communications beyond the drug facts label. *(Also see "Room For Innovative Switches Could Lurk In Existing FDA Framework" - Pink Sheet, 29 Oct, 2014.)*

In 2015, Mahecha acknowledged that despite the NSURE initiative and a "favorable" regulatory environment for the products, the switch landscape has been "quiet." At the time, she noted the high costs of making a switch – including the product's application and then it's marketing and advertising – as one factor slowing the pace of new switches. *(Also see "Merck Silence On OTC Singulair Speaks Volumes On Switch Outlook" - Pink Sheet, 10 Dec, 2015.)*

She also noted Kline's FutureView Forecasting Model online tool that uses basic drug description ajnd information on manufacturers and countries to calculate estimates of a "probability of switch" and post-switch sales.

From the editors of the Tan Sheet. Published online July 5, 2017

Switch Categories' Safety Questions

CATEGORY (INDICATION)	FDA'S SAFETY CONCERN
Acne	Teratogenicity from systemic absorption of topical retinoids
Allergy	Growth suppression from systemic absorption of intranasal steroids
Benign prostatic hyperplasia	Masking of prostate cancer with alpha blockers
Digestive products	Long-term use of PPIs
Erectile dysfunction	Cardiovascular risk with PDE5 inhibitors
Migraine	Cardiovascular risk with triptans
Overactive bladder	Masking of bladder cancer, kidney problems and prostate cancer in men with symptoms similar to OAB
Sleeping aids	Addiction potential
Skin rash/eczema	Growth suppression from systemic absorption of topical steroids
Topical pain relievers	Cardiovascular risk from systemic absorption of topical NSAIDs

Source: Kline & Co.

Clock Ticks On Adding OTC Monograph Reform To FDA User Fees Bill

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Time is running short and competing issues are stacking high for adding OTC monograph reform and user fees to legislation reauthorizing FDA's existing user fee programs for another five years.

With Congress leaving Washington during the week of Independence Day and for much of August, few days remain for House and Senate committees to consider adding to language from Sens. Johnny Isakson, R-GA, and Ben Casey's, D-PA, OTC discussion draft to the pending reauthorization legislation – H.R. 2340 and S. 934.

Failure to reauthorize the user fee programs agreements by late July would prompt FDA to send layoff notices to more than 5,000 employees to notify them that they may lose their jobs when the federal fiscal year ends Sept. 30.

The Consumer Healthcare Products Association, which negotiated with FDA on terms of the monograph proposal included in the draft, is joined by medical and advocacy groups the American Academy of Pediatrics, Society for Maternal-Fetal Medicine, American Public Health Association, March of Dimes, Pew Charitable Trusts and National Association of County and City Health Officials in urging members of Congress to include the changes in the user fee reauthorization legislation.

The groups continued urging passage in their latest letter, dated June 14, to Isakson, Casey and Senate Health, Education Labor and Pensions Committee Chairman Lamar Alexander, R-TN, and ranking member Patty Murray, D-WA. They say "monograph reform can and should be included within the Food and Drug Administration Reauthorization Act (FDARA) of 2017," and FDA, the pharma industry "and public health stakeholders are in clear consensus that OTC drug regulation reform is long overdue and should be a top priority for this Congress."

However, FDA's OTC monograph problems likely are not a priority for Congress currently. An overhaul of the Affordable Act – either repeal and replace or enacting changes – is the health care-related topic dominating Congress members' attention. Imposing drug-pricing standards has emerged as one contentious topic in discussions on legislation targeting changing or repealing the ACA. *(Also see "Drug Pricing Hearing In Senate Postponed, Handing Innovators Another Victory" - Pink Sheet, 29 Jun, 2017.)*

When the House and Senate resume meeting July 10, additional hearings and ongoing investigations into Russian hacking into US elections and on potential illegal collaboration with Russian officials and businesses by people associated with President Trump's campaign along with work on developing and approving FY 2018 appropriations for FDA and other federal agencies will dominate members' time.

Doing anything more than passing FDARA only to continue FDA's existing user fees programs could be too much to expect, says Kurt Karst, a food and drug lawyer following FDARA discussions.

"At some point it will come down to, just get it out," said Karst, a director at Hyman, Phelps & McNamara P.C. in Washington.

Backing from CHPA and its allies is crucial to any chance for adding the monograph reform language to FDARA, and Congress is capable of surprises.

"I certainly think [CHPA's lobbying] helps. But the timing doesn't help," Karst added in an interview.

CHPA is keeping its eye on the goal. "We are optimistic that OTC Monograph reform will move forward along with the FDA Reauthorization Act," the group told the Pink Sheet.

Pew, the lead in contact with Congress among the groups backing monograph reform, points out making the changes has bipartisan support. "We have confidence that Congress will act before the end of 2017 to address outdated and inefficient OTC regulation under the current monograph system," said Kirsten Moore, PEW's health care products project director.

Isakson and Casey propose that manufacturers have two tracks for proposing changes to OTC products marketed under the monograph system: one for adding new medical conditions treated by the ingredients, which would be eligible for exclusivity when clinical trials are required, and another for most other types of changes. The senators in early May released an initial discussion draft and in early June distributed another version that had been cleared of notes and questions. *(Also see "OTC Monograph Reform Proposal*

Offers Two-Tier Approach" - Pink Sheet, 30 May, 2017.)

Similar to the Sunscreen Innovation Act Congress passed in 2015 to encourage adding new ingredients to the OTC sunscreen monograph, the discussion draft proposes deadlines for FDA reviews for the other monograph categories.

Total annual user fees of $22m to $34m from OTC manufacturers – primarily from facility registrations – are among the draft's proposals. Fees would also be raised when companies request changes via the monograph system. *(Also see "OTC Monograph User Fees Up To $34M Floated In Senate Discussion Draft" - Pink Sheet, 30 May, 2017.)*

FDA launched the monograph program, following congressional authorization, in 1972 as a system for allowing OTC ingredients generally recognized as safe and effective for their intended uses to remain available and for offering drug firms and other parties, including the agency, a process for proposing additions of more ingredients or indications. However, the program has been stalled for much of its 45 years and FDA and industry stakeholders identified reforming the program as a nonprescription sector priority well before they began negotiations on a proposal in June 2016. *(Also see "'Real Challenge' To Improve OTC Monograph Program Without User Fees – FDA" - Pink Sheet, 13 Jun, 2016.)*

From the editors of the Tan Sheet. Published online July 6, 2017

FDA's Unger On Exondys Approval As Precedent: 'We Hope Not'

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Ellis Unger, Director of FDA's Office of Drug Evaluation I, is still not happy about how the accelerated approval of **Sarepta Therapeutics Inc.**'s *Exondys 51* (eteplirsen) played out and he's not pulling any punches about his feelings on the review.

A remarkable panel at the New York Academy of Sciences on June 22 featured brutally honest yet measured commentary on the lessons from the eteplirsen review by outgoing Sarepta CEO Ed Kaye, Parent Project Muscular Dystrophy President Pat Furlong, investor David Sheer, and Unger, who was the prime mover within FDA for raising the review to institutional importance. He appealed the approval all the way to the FDA Commissioner.

Lost in the controversy surrounding the approval of eteplirsen is that the drug's staunchest opponent for its accelerated approval – Unger – has been a very engaged, hands-on manager at FDA in the adoption of regulatory flexibility for rare disease drug development at FDA.

For example, Unger was deeply involved in a landmark FDA workshop on "Complex Issues In Developing Drug and Biological Products for Rare Diseases" in January 2014. It was at that meeting where Unger first expressed his philosophy of broad flexibility in the development strategies and approval of drugs for rare diseases where there is an unmet need.

In March 2015, he was extremely involved in an FDA/NIH technical scientific workshop on dystrophin protein quantification methodologies.

Unger introduced himself as a longtime researcher with experience at NIH prior to moving up the ranks at FDA to head one of FDA's most important Offices.

"I spent 14 years at NIH doing what is now called translational research – preclinical research – and learned firsthand how bias can make a huge impact on science and lead to false negative results. It's amazing."

Lost in the eteplirsen controversy is that the drug's staunchest opponent for its accelerated approval – Unger – has been a very engaged, hands-on manager at FDA in the adoption of regulatory flexibility for rare disease drug development at FDA.

The first question asked by moderator Meg Tirrell (CNBC) was whether Sarepta is a precedent that other drug companies will follow as a model? Unger was characteristically direct: "Well, we hope not; and we haven't seen any but we could."

Unger described eteplirsen as an accelerated approval based on a surrogate marker of the amount of dystrophin produced and the amount was small.

"The point is that being a very small amount of a crucial substance, if that's enough for accelerated approval, then what we worry about is that companies come in, gene therapy or cell therapy and say 'here's the missing protein in disease X and our therapy produces a tiny amount and you approved eteplirsen based on a tiny amount of dystrophin so how is it you can't approve our drug?' That's been the worry, but so far we haven't seen anyone try to do that."

Kaye, who carried the application through to approval following the departure of Chris Garabedian, said: "I would agree with Dr. Unger, I don't think this has changed anything dramatically."

Then talk turned to the April 2016 Peripheral & Central Nervous System Drugs Advisory Committee review and the presentation by a patient advocate during Sarepta's formal sponsor presentation to the committee.

"That was unprecedented actually and we never had a public comment period that long, Unger said. "I hope we never do again. It was really a circus," Unger said. That drew a caustic rebuke later during the NYAS from an audience member, showing that nine months and commercial availability of *Exondys 51* have not salved all of emotions from the review. "There's patient advocacy and then there's patient advocacy. Even doubters have become very impressed with the utility and power of patient advocacy."

Unger praised FDA's formal patient input meetings created by the enactment of PDUFA V. "These patient focused drug development meetings we've been having at FDA have been great. These patient advocacy meetings are best for asking patients what they care about, what are the benefits they care about, what don't they care about, what are the harms that are worrisome and what are the harms that are acceptable."

The patient advocacy for eteplirsen "went over the line," however. Unger then described how the patients were particularly close to the company and were coached by a consultant during open testimony.

"But the data showed that, unfortunately, patients were deteriorating and when we asked the patient representative on the advisory committee to try and reconcile why the data showed deterioration but all the kids were getting up to the microphone saying they were doing so much better, he began to cry – and so did I."

Noting all of the information is in the public record following the appeal of the decision up to then-FDA Commissioner Robert Califf, Unger said FDA received approximately 4,000 emails, "some were vulgar, some were threatening."

He continued: "I won't say this was or was not a coincidence but there were a couple of members on the review team in the neurology division, very talented people, who are gone. One most certainly felt threatened by the emails and that individual is gone and it is very difficult to replace this kind of talent. This was not constructive."

Unger said the approval of eteplirsen in the end was based on muscle biopsies, that are very painful for the patients, typically young boys, who have to go under general anesthesia – "it's a big deal, but if they had figured out at the beginning, they could have done needle biopsies instead of open biopsies."

Ignoring early advice from FDA to the sponsor was a consistent theme in Unger's comments on the review, whether for the dose and trial design or how data were publicly released. He called the first report of eteplirsen increasing dystrophin production by almost 50% (that was later found to be inaccurate) as the key development that changed the paradigm of the eteplirsen review and that it gave patient advocates a "shot of adrenaline."

"I feel so bad for the parents because the drug has no toxicity. When people develop drugs and there's no toxicity and the efficacy is not that great, we say 'you've got to go to a higher dose – push the dose." Unger added that animal data testing higher doses showed increased expression of the protein.

"To me, it's extremely sad that patients are getting this dose of the drug that we know is producing 1,000th of what a normal person would produce that's all they're getting and a higher dose could produce much, much more. So that's where I am."

Califf, in the audience for the session, commended the panel for the honest discussion and pointed out a key reason why etelplirsen should not be viewed as a precedent in drug development. He said that he could not find a single person at FDA who felt the drug was well-studied.

BioMarin Pharmaceutical Inc.'s drisapersen, which was issued a complete response letter by FDA, came up during the panel discussion as a drug that was too toxic and therefore the agency rejected it.

Unger made clear it was a lack of efficacy and not safety that led to the CRL. "I wouldn't say that," Unger responded referring to the safety of the drug as the reason drisapersen was not approved. "I would say that for a disease like DMD, with at the time no treatments, our tolerance for risk is extremely high. My philosophy is – and I'm the person charged with approving drugs for these diseases – you put it in the label. If there are risks, you put it in the label, you let the buyer understand what the risks are. We've heard over and over again from various groups, when you're facing a death sentence, you're not interested in paternalistic behavior by the FDA telling you what you can and what you can't have."

"On BioMarin, I don't think [the toxicity] had any effect on us. That would not have precluded the approval."

Towards the end of the panel session, an audience member criticized Unger for using the term 'circus' to describe the Sarepta advisory committee.

"I understand what you're saying, and in some sense I agree with you, but the reason I used 'circus' is because when the Deputy Director of the Neurology Division [Eric Bastings] told a very personal story of tragedy, he was heckled. The communication goes both ways. It was very difficult," Unger answered. "The reason I use the word circus was because of the catcalls and the heckling. It was very disheartening. And I apologize for using that word but that's where that came from."

From the editors of the RPM Report. Published online July 2, 2017

Recent And Upcoming FDA Advisory Committee Meetings

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

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