Pink Sheet
pink.pharmamedtechbi.com Vol. 79 / No. 37 September 11, 2017
Pharma intelligence informa

Patient Advocates Continue To Push US FDA For Central Office

DERRICK GINGERY derrick.gingery@informa.com

In a March notice, FDA floated the idea of creating a patient affairs office as a central entry point, but its plans going forward are unclear.

Shutterstock: kamol dechasathian

Advocates will not let the US FDA forget about the virtues of creating a central office for the agency's patient affairs operations.

Several patient groups met with Principal Deputy Commissioner Rachel Sherman and colleagues on Aug. 25 to talk about "patient engagement," according to FDA's public meeting calendar. Among the meeting topics was the agency idea to create an Office of Patient Affairs, according to Mark Fleury, policy principal at the American Cancer Society Cancer Action Network (ACS CAN).

Fleury told the Pink Sheet that during the meeting, he and others present "encouraged the agency to move forward with its proposal to develop a new office."

FDA floated the idea of creating a patient affairs office in a March Federal Register notice and asked for stakeholder comments. The agency said the new office would provide a single entry point for its patients, as well as handle related activities across FDA's medical product centers and other offices. *(Also see "US FDA Patient Affairs Office Could Accelerate Involvement With 'Central Entry Point'" - Pink Sheet, 14 Mar, 2017.)*

FDA's intentions for the Office of Patient Affairs idea remain unknown. The agency said that it did not have any updates to share on its status and noted the meeting with the advocates was part of its ongoing effort to hear patient views.

Fleury was joined at the meeting by Paul Melmeyer, director of federal policy for the National Organization for Rare Disorders (NORD) and Susan Peschin, president of the Alliance for Aging Research, according to the FDA calendar entry.

Peschin said the group reiterated its interest in ensuring that the new office would be "additive to existing efforts in patient engagement."

During the meeting, the agency said it "expressed its ongoing commitment to transparent, streamlined patient communication between FDA offices and patients."

"The FDA has long recognized the importance of engaging with patients, caregivers, and their advocates in the medical product development process and is committed to understanding this better. This meeting was part of those efforts," FDA said.

The office also would help ensure requests were routed to the proper people within the agency and create a scalable communications platform for communicating with stakeholders.

The new organizational structure was viewed as another potential expansion of FDA's ongoing patient engagement programs. Among them was the patient-focused drug development initiative, where the agency invited patients and advocates to meetings on various diseases to discuss existing treatments and unmet needs. *(Also see "Patient-Focused Drug Development At 10: Where Does It Go From Here?" - Pink Sheet, 20 Oct, 2014.)*

FDA said in May that it also was develop-

CONTINUED ON PAGE 4

BROUGHT TO YOU BY THE EDITORS OF SCRIP REGULATORY AFFAIRS, THE RPM REPORT, TAN SHEET, GOLD SHEET, PINK SHEET DAILY AND PINK SHEET

INVESTOR FORUM

October 17-18, 2017 | The Westin St. Francis, San Francisco, CA

Conference features:

- **Company presentations** given by over 150 early and late-stage private biotech companies and emerging public companies.
- **Fireside Chats and expert-led panel discussions** on the latest market and investment opportunities with emphasis on drug and technology development.
- More than 2,100 **BIO One-on-One Partnering™** meetings.
- **Buzz of BIO competition** recognizing "Early Stage Entrepreneurs", "Late Stage Leaders" and "Diagnostics and Beyond."

The BIO Investor Forum is an international biotech investor conference focused on investment trends and opportunities in life sciences, with unbiased emphasis on venture-stage growth and emerging public companies as well as those poised to join the growth "watch list" in 2018.

Complimentary registration is available for investors. For more information and to register for the event, please go to

bio.org/investorforum

Accelerate Discovery. Amplify Returns.


6


7


13

exclusive online content

Global Pharma Guidance Tracker – August 2017
https://pink.pharmamedtechbi.com/PS121476
Stay up to date on regulatory guidelines from around the world, with the Pink Sheet's Guidance Tracker.

France In Talks With BeNeLuxA Access To Meds Coalition; Group Plans Expansion Beyond EU
https://pink.pharmamedtechbi.com/PS121489
The BeNeLuxA collaboration for sustainable access to medicines may soon expand further. Future partners could include France and non-EU markets.

Gene Therapy Platforms May Require Less Preclinical Data, Gottlieb Says
https://pink.pharmamedtechbi.com/PS121494
US FDA's preclinical policies should be 'more closely matched to the complexion of modern technologies,' commissioner explains.

FDA Soliciting Broad Range Of Comments From Industry On Regulatory Reform
https://pink.pharmamedtechbi.com/PS121490
FDA is addressing regulatory reform as part of President Trump's "two-for-one" executive order, and seeks industry comments to supplement the effort.

Amarin's Omega-3 Fair Trade Complaint Questions US Dietary Ingredient Standards
https://pink.pharmamedtechbi.com/PS121477
Amarin's recent fair trade complaint targetting purified EPA dietary supplements and formulations also raises broader questions about using synthetic dietary ingredients in consumer supplements and the extent to which a substance's identification in an IND precludes subsequent use as a dietary ingredient.

Don't have an online user account?
You can easily create one by clicking on the "Create your account" link at the top of the online page.
Contact clientservices@pharmamedtechbi.com or call:
888-670-8900 or +1-908-547-2200 for additional information.

inside:

CONTINUED FROM COVER

ing a Patient Engagement Collaborative, which is expected to include regular meetings between agency officials and patients to discuss improvements to the engagement effort. *(Also see "US FDA Planning Another Patient Group To Boost Involvement" - Pink Sheet, 15 May, 2017.)*

STAKEHOLDERS MOSTLY LIKE THE IDEA

More than 80 organizations, including ACS CAN and NORD, submitted a joint statement to FDA's docket applauding the Office of Patient Affairs idea.

The groups said the proposal will be essential to the success of FDA's patient engagement program, but also could be improved, in part to ensure the office "does not act as a barrier to existing relationships."

The new office could become the central contact point for expanded access questions and requests, the patient groups suggested. Peschin said the office's potential role as an educational resource for expanded access was one of the areas the advocates highlighted during the meeting with Sherman.

Expanded access has gained attention in recent months amid efforts to expand the programs. *(Also see "FDA Policy Says Right-to-Try Talks Are Between Providers, Sponsors" - Pink Sheet, 17 Aug, 2017.)*

The National Health Council did not want patient engagement to become "siloed" within the new office. The group also suggested in its comments that the new office must be fully staffed and trained to ensure responses are not delayed.

"Simply moving current point persons for patient engagement efforts from across the Agency into one office without improving the FDA's overall ability to effectively and efficiently respond to patient engagement requests … will do little to provide a more transparent, accessible, and robust experience for patient communities," NHC wrote.

PhRMA said FDA should use the patient affairs office to cut redundancy within its patient engagement activities.

Several companies and industry groups also praised the patient affairs office idea in comments, but also sought more clarity on its operations.

The Pharmaceutical Research and Manufacturers of America (PhRMA) said FDA should use the patient affairs office to cut redundancy within its patient engagement activities.

"OPA could take the lead on numerous patient education activities designed to enhance health literacy and patients' understanding of the role FDA plays in drug development and regulation, including lay-friendly plain language definitions of terminology, how FDA performs its benefit-risk assessments, and how direct-to-consumer advertising is regulated," PhRMA wrote in its comments. "Ensuring that agency communications are easily understood by a variety of audiences could be an effective and important role for OPA."

The Biotechnology Innovation Organization asked in its comments for more information on governance, in part to ensure the office would not conflict with the PDUFA VI agreement embedding FDA rare disease experts with review divisions. *(Also see "Rare Disease Integration Into FDA Reviews Will Grow Under PDUFA VI" - Pink Sheet, 18 Jul, 2016.)*

ONE OF SHERMAN'S FIRST BIG MEETINGS SINCE PROMOTION

The meeting with patient advocates was one of Sherman's first since becoming the number two leader at FDA.

On Aug. 17, the agency announced that she was named principal deputy commissioner, the first permanent holder of the position since 2011. *(Also see "Gottlieb Adds A No. 2: Sherman Is US FDA Principal Deputy Commissioner" - Pink Sheet, 21 Aug, 2017.)*

Her involvement signals that under new Commissioner Scott Gottlieb, patient involvement will remain a priority.

The effort may have suffered last fall after the massive patient lobbying effort leading up to FDA's controversial approval of **Sarepta Therapeutics Inc.**'s Duchenne muscular dystrophy treatment *Exondys 51* (eteplirsen).

PTC Therapeutics Inc.'s DMD candidate *Translarna* (ataluren oral suspension) is set for an advisory committee meeting in late September, which also could include a substantial contingent of patients and advocates. *(Also see "Once More Unto The Breach: PTC's Duchenne Drug Translarna Gets Advisory Cmte." - Pink Sheet, 22 Aug, 2017.)*

Published online September 5, 2017

LET'S GET SOCIAL

We are tweeting, liking and sharing the latest industry news and insights from our global team of editors and analysts, join us!

@PharmaPinksheet

© Informa UK Ltd 2017

FDARA, 21st Century Cures And The Era Of Perpetual FDA Reform

MICHAEL MCCAUGHAN pinkeditor@informa.com

Shutterstock: Derrick Larkin

The relatively straightforward reauthorization of the Prescription Drug User Fee Act – and the host of companion user fee programs added to FDA since PDUFA was first created in 1992 – wouldn't have been so simple without the 21st Century Cures Act.

The Cures law, signed in December 2016 more than two years after a push to overhaul biomedical innovation policies that began in the House Energy and Commerce Committee leadership in 2014, helped secure passage of FDARA in two important but very different ways.

First, many of the regulatory reforms that would normally have been included in the user fee omnibus bill in 2017 were instead enacted ahead of time as part Cures. That effort allowed for a more tightly focused user fee bill – clearing out much of the legislative work that would have been extremely difficult to accomplish with a new Congress and new federal administration in 2017, particularly giving the dominant distraction of the debate over repealing the Affordable Care Act.

But the signing of Cures was also significant in helping reinforce an important message to legislators and outside advocates in the context of FDARA: it demonstrated that Congress can and will revisit important FDA-related topics outside of the every-five-year user fee cycle.

One of the many ways PDUFA transformed FDA was by creating a five-year reauthorization cycle that demanded legislative attention to the agency at regular intervals. That was hailed at the time as an improvement over the historical model of legislating dramatic FDA reforms in times of perceived crisis – and then neglecting the agency until the next crisis came. Instead, Congress could periodically review the agency and make smaller, incremental changes.

But that also created tension in the reauthorization process. There has been remarkable bipartisan consensus on the urgency of enacting the bills in a timely fashion – but also considerable pressure to make sure that the once-every-five-year legislative train doesn't leave the station until every possible passenger has a chance to board.

The challenge in 2017 was only magnified by the calendar. For the first time, the user fee reauthorization was scheduled to coincide with the first year of a new presidency. Even without the unexpected dynamics of a Donald Trump administration, that promised to make the legislative dynamics challenging.

Trump's unexpected victory, in fact, helped secure enactment of Cures in the lame duck legislative session that followed the election. *(Also see "The Unlikely Savior Of '21st Century Cures' Is Donald Trump" - Pink Sheet, 7 Dec, 2016.)* And that in turn helped congressional leadership provide credible assurances to their colleagues and outside advocates that work on bipartisan proposals could continue after FDARA, and that they don't need to hold up FDARA to make sure they have a vehicle at the ready.

In fact, there are two precedents to point to since the 2012 user fee bills: the Drug Quality and Security Act passed in 2013 and the Cures Act in 2016. While DQSA is primarily remembered now as the response to the drug compounding controversy, it actually began as an effort to implement track-and-trace provisions that weren't ready in time for the 2012 PDUFA cycle.

The message that there will be other chances to pass FDA-related reforms, however, is something of a double-edged sword for FDA and industry. The good news is that the reassurances worked: the user fee omnibus passed without too many add-ins from Congress – and well ahead of the fiscal year-end deadline. FDARA is, in fact, the "cleanest" user fee reauthorization since the 2002 PDUFA III agreement, which passed as almost a stand-alone measure added into the bioterrorism preparedness law enacted that year.

The bad news, though, is that enactment of the FDA Reauthorization Act won't mean an end to the debate over potentially unwelcome regulatory changes in the months ahead – and it almost certainly won't mean an end to new deadlines and deliverables for FDA even as it attempts to follow through on implementing the user fee programs.

For biopharma companies, the most important topics that were successfully deflected out of FDARA were on the broad theme of drug pricing and a more narrowly focused effort to open up access to unapproved medicines (so-called "Right-to-Try" measures). Both were kept out of the bill – but also kept alive for further attention. *(Also see "Implementing User Fees Should Be Lighter Lift For FDA This Time Around; Bill Heads To White House" - Pink Sheet, 3 Aug, 2017.)*

There are clearly areas of bipartisan consensus in favor of reforms, including topics like lab-developed test, cosmetic safety and the OTC monograph system. In fact, FDA and industry completed an agreement on an OTC user fee program that appears ready to enact. *(Also see "Waiting For Congress: Reforming, Paying For FDA OTC Monograph Program" - Pink Sheet, 23 Aug, 2017.)*

For its part, the House had several separate priority items that were stripped out of the bill – including efforts to address off-label promotion rules. That at least raises the potential that another FDA bill could be pulled together out of pieces that didn't make it into FDARA.

And it also raises the possibility that the five-year legislative cycle for FDA reforms that began in 1992 may be over. FDA reform may now be an almost annual event.

From the editors of the RPM Report. Published online September 5, 2017

Avoid 'Political Games' Or Risk EMA Losing Most Of Its Staff, Italian Industry Head Warns

IAN SCHOFIELD ian.schofield@informa.com

Shutterstock: jivacore

"We must choose a city that meets all the objective criteria" – Massimo Scaccabarozzi, Farmindustria president

The head of the Italian pharmaceutical industry body, Farmindustria, has called on the EU to draw up a shortlist of countries bidding to host the European Medicines Agency after Brexit, saying that otherwise the selection process could be dominated by "political games," with the EMA at risk of losing most of its staff if they don't want to move to the new location.

Janssen Italy managing director and Farmindustria president Massimo Scaccabarozzi naturally enough feels the northern Italian city of Milan would be a good choice for the EMA's future seat. He says it is vital to ensure that the decision, which will be made in November, is based firmly on "objective and valid" criteria. He fears, though, that political bargaining might win the day.

The six criteria on which the new location will be chosen were formally published by the European Council on Jun. 22. As well as five "objective" criteria, such as international connectivity, suitable premises and educational facilities for families of EMA employees, the list includes "geographical spread" – i.e., the need to take account of the fact that some member states do not currently have an EU agency.

Most of these countries are in eastern Europe, and some of those that bid for the EMA – including Bulgaria, Croatia and Slovakia – cited the geographical spread factor when explaining why they should be chosen to host the EMA. By contrast, other member states, such as Belgium, Denmark, Ireland and the Netherlands, said this consideration should apply only in the case of new agencies, not an established one like the EMA where business continuity is paramount. *(Also see "Bids For EMA Show East-West Split Over Principle of Fair Spread Of Agencies" - Pink Sheet, 7 Aug, 2017.)*

Fears have already been expressed that the geographical criterion could lead to political horse-trading trumping the "objective" criteria, and that the EMA's ultimate destination will have a bearing on how many employees decide to remain with the agency.

A total of 19 countries have formally bid to host the EMA. Scaccabarozzi suggested that many of them stood no chance and had entered the fray simply to be able to withdraw at the voting stage and support a given country, in the expectation of something in return. But the EMA's future location, he said, had to be chosen on the basis of objective and valid criteria, not by supporting one country in exchange for a "favor".

In an interview with the *Pink Sheet*, Scaccabarozzi said that the "geopolitical criterion" should be abandoned so as to guard against the EMA ending up in "a city where nobody from the EMA wants to go."

If this happened, "800 people" might refuse to move with the EMA, and it would no longer be able to do its work, so "we must choose a city that meets all the objective criteria," he said. The EMA is a "very, very important agency and it would be a shame if, for non-objective reasons, the EMA should disappear or lose value."

Similar concerns have been expressed by the EMA itself, which last month said it was planning for "potentially significant" job losses depending on its future location, and that "unexpected higher, faster or more permanent loss of staff as a consequence of the agency's relocation may lead to a situation in which EMA's operations can no longer be maintained." *(Also see "EMA Suspends Some Activities & Warns That High Job Losses Could Halt Its Operations" - Pink Sheet, 2 Aug, 2017.)*

Scaccabarozzi suggested that a committee be formed to draw up a shortlist of, say, four or five candidates "based not on

© Informa UK Ltd 2017

political but on objective criteria." As to how this suggestion might be received at EU level, he said he would like politicians and diplomats from Italy and other countries to push for such a shortlist.

Milan, he believed, would "certainly make it" onto the list because it met all the criteria. It had good air connections, housing and schools, and there was a suitable building ready for the EMA to move straight into.

EP PRESIDENT ON THE RELOCATION

Other Italian voices have been calling for the decision to be taken on the basis of objective criteria. The president of the European Parliament, Antonio Tajani, recently met with Guido Rasi, executive director of the EMA, to discuss the EMA's role and the relocation question.

"Choosing the new headquarters of the EMA must be based on objective criteria drawn up at the European level whose aim must be to make its running as economical and efficient as possible, in the interests of our citizens," Tajani declared, adding: "Some candidate cities fully fulfil the criteria required."

Tajani went further, claiming that the European Parliament would "ensure that the new headquarters will be chosen with due regard for these objective criteria, in full transparency, in the interests of safeguarding the health of our citizens while promoting innovation."

Just how the parliament would go about ensuring this happened is unclear, though, given that it has no formal role in the selection procedure, which is now under way after bidding ended on July 31.

The European Commission is currently assessing the 19 bids, and will submit its assessment to the council by Sept. 30 and make it publicly available. The final decision on the EMA's new location will be taken by the other 27 EU member states, with the vote scheduled to take place in the margins of the General Affairs Council (Article 50) meeting on Nov. 15.

From the editors of Scrip Regulatory Affairs. Published online September 5, 2017

UK Urged To Take Lead on Novel Clinical Trials, Foster Digital Tools

IAN SCHOFIELD ian.schofield@informa.com

Shutterstock: kentoh

The government needs to support efforts to increase the number of clinical trials conducted in the UK by 50% over the next five years, especially "change of practice" trials and those with novel designs, in order to attract more inward investment in clinical research and compete globally for industry and academic studies at all trial phases, according to the pharmaceutical industry.

The call comes in the UK's Life Sciences Industrial strategy, which was produced by Professor Sir John Bell based on ideas submitted by life science companies and published on Aug. 30.

> "The UK is well positioned to deliver a host of new innovations such as the use of digital tools"
> – Life Sciences Strategy

While not specifically mentioned in the strategy, the proposals are framed at least in part to strengthen the UK's attractiveness as a trial location following its decision to leave the EU – a decision that many fear could lead to a fall in clinical trial activity.

The strategy, which incorporates input from a range of stakeholders including global companies such as AstraZeneca, Johnson & Johnson, MSD, GSK, and healthcare groups, as well as SMEs and charities, is the prelude to a "sector deal" for the life sciences industry. It includes a number of proposals regarding the need for continued alignment in pharmaceutical regulation between the UK and EU after Brexit. *(Also see "UK Life Science Strategy Urges Continued Regulatory, Research Ties With EU" - Pink Sheet, 31 Aug, 2017.)*

In the section on clinical trials, the strategy says that the UK has a number of clinical trial networks that have enabled the efficient delivery of large-scale trials, as well as a "globally leading" position in translational medicine, with around 35,000 patients being enrolled into commercial trials in 2016/17.

But there is still "considerable room for improvement in translational science to enhance the UK's capability to attract more clinical trials from industry – a ma-

jor source of inward investment in the life sciences space," it declares. For example, there are still barriers in terms of administrative burden and "poor digital evidence collection infrastructure."

Nonetheless, the strategy says the UK is well positioned to deliver "a host of new innovations" such as the use of digital tools to improve the quality of data collected and to speed up recruitment.

To take advantage of this position, though, the National Health Service needs to get better at running complex trials – possibly with novel trial designs – in diseases in smaller numbers of patients and at recruiting those patients in more targeted ways, for example using genomics.

And if the UK is to conduct more complex and innovative trials, the regulatory agency, the MHRA, needs to "continue engaging with sponsors to assist with innovative protocol designs and should facilitate efficient approval of complex trials and amendments to such trials, for example, to add new arms."

The strategy also recommends that the UK should attempt to lead innovation in clinical trial methodology, such as "basket trials" (for example patients with different types of cancer but a common mutation), and to use routine genomic analysis to make trials more targeted, smaller and more likely to deliver high efficacy.

DIGITAL DYNAMICS

Digital technologies will of course be an increasingly vital component of clinical trials in future, and the strategy suggests that there are "considerable opportunities" for the National Institute for Health Research and the NHS trial infrastructure to "distinguish itself from other clinical trial environments by moving rapidly to take advantage of the increasingly mature digital capabilities in the NHS."

Digital recruitment has already begun using the Clinical Practice Research Datalink, which has developed an integrated clinical trials platform to support real-world clinical studies throughout the drug development pathway. To date, 19 of the top 20 global pharmaceutical companies have used CPRD data services.

Digital tools also provide unique opportunities for measuring outcomes and generating much richer datasets to demonstrate utility of healthcare interventions, the strategy notes. "These assets, along with the implementation of digital tools to provide the environment for paperless trials will all greatly enhance the quality of information obtained by commercial partners when operating in the NHS and will greatly speed up both the recruitment and the implementation of clinical trials, including the use of electronic data capture and informed consent, thus significantly reducing cost."

EARLIER TRIALS

The strategy also addresses issues earlier on in the drug development pathway, pointing out that there are examples of strong clinical trial networks that have been able to create rapid and effective exploratory development programs in particular disease areas. These include the NIHR Clinical Research Network, NIHR Translational Research Collaborations, the NIHR Clinical Research Facilities network and the Experimental Cancer Medicine Centres network.

"It is therefore recommended that funding agencies look again at how such early-phase networks can be identified and supported, enhancing the ability of the UK to provide useful early-stage data to the life sciences industry," it says. "A set of early clinical trial networks capable of rapid patient recruitment backed by strong science capability would be a great attraction to industry."

Further back still in the R&D pipeline, the strategy outlines industry's concern that the UK is still not extracting the full value from discovery research by comparison with international hubs, and suggests the setting up of a "translational fund" that would support the pre-commercial creation of "clinically-useable molecules and devices" that could then be explored in preclinical and early clinical studies.

"Testing such targeted products in a translational setting would produce insights that would de-risk the creation of small companies and also enhance the early translational capabilities of clinicians and investigators," it says.

Other than programs supported by Cancer Research UK, "few if any academic groups are capable of the drug discovery necessary to create clinically-useable molecules but these can be readily produced for academics by the Contract Research Organisation (CRO) industry," the strategy notes.

"By creating an opportunity for investigators to undertake these early-stage investigations with molecules made by CROs, an important step will be taken to ensure that biotechnology companies are not started too early as, historically, they have been in the UK. By ensuring that there is more clinical data, a major step will be taken in reducing the risk and enhancing the chances of success of biotechnology companies."

Published online September 4, 2017

What's New Online?

- Quicker access to crucial information and insights
- User-friendly, responsive design
- Streamlined navigation, design and menus
- Robust search capability
- And much more, please visit:

pink.pharmamedtechbi.com

Pink Sheet
Pharma intelligence | informa

© Informa UK Ltd 2017

BRAZIL: Spending On Meds Acquired Through Law Suits Rockets

FRANCESCA BRUCE francesca.bruce@informa.com

Brazil's federal health ministry is spending more and more on medicines that patients have won access to via the courts, says an audit by the General Accounting Office (TCU). Shire's *Elaprase*, Alexion's *Soliris* and Biomarin's *Naglazyme* commanded the biggest spends between 2010 and 2015.

The audit authors warn that the so called 'judicialization of health' is a widening vicious circle that diverts funds from other treatments.

For some years patients have been resorting to law suits to secure the treatments that they want. This is possible because according to Brazil's constitution, all citizens have the basic right to healthcare. The constitution does not stipulate how this should work in practical terms and it fails to set out any limits on the provision of healthcare.

If a product is made available through the national health system, the SUS, it should be available and accessible to all Brazilians. Most cases arise when a product is not available through the SUS, which may be because it has been excluded from the system or because it has not been assessed for inclusion. And in some cases, patients seek access to experimental or off-label drugs or those that are not registered with the medicines regulator, ANVISA. Success rates for such law suits are high as judges tend to side with patients. Companies, lawyers, patient groups and healthcare professionals have been accused of exploiting and profiting from the system.

According to the audit, in 2008, the health ministry spent R$70m ($22.3) on products secured through law suits. By 2015 the figure jumped to more than R$1bn. From 2010 to 2015, the health ministry spent R$s2.7bn at the behest of the courts. Some 54% (R$1.49bn) was spent on just three medicines: Elaprase (idursulfase), **Shire PLC**'s enzyme replacement therapy for Hunter syndrome (mucopolysaccharidosis type II or MPS II); **BioMarin Pharmaceutical Inc.**'s Naglazyme (galsulfase), which is used to treat MPS VI, or Maroteaux-Lamy syndrome; and **Alexion Pharmaceuticals Inc.**'s Soliris (eculizumab) for treating paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. At the time the drugs were not listed on the SUS, and Soliris was not yet registered with ANVISA. These figures do not include spending by state authorities, which is also on the rise.

SURGE IN SPENDING

The audit recognizes several reasons for the jump in spending. It explains that new technologies and new medicines have entered the market at a greater speed than the public health system can cope with. Secondly, the revolution in information technology, namely the internet, means that news of these new technologies travels quickly to countries where the products are not available.

Shutterstock: AMA

> "This loss has the potential to destabilize the public health network, leading to even more judicialization of products that should be provided regularly by SUS."

The number of law suits seeking to have these medicines imported has increased, says the audit. In addition, high success rates and ease of access to the judicial system encourage yet more cases. The audit adds that there appear to be networks between patients, lawyers, doctors and the pharmaceutical industry which try to encourage more cases.

The impact of these suits spells bad news, says the audit. The increase in spending is irreversible in the short term because of the volume of new cases combined with obligations to maintain treatment for patients who have already won their law suits. "Resources are diverted away from elsewhere in the public health system to the detriment of planning and managing budgets. "This loss has the potential to destabilize the public health network, leading to even more judicialization of products that should be provided regularly by SUS."

From the editors of Scrip Regulatory Affairs. Published online September 1, 2017

FDA Wins Abilify Exclusivity Battle; Court Rejects Otsuka's 'Legal Equivalence'

BRENDA SANDBURG brenda.sandburg@informa.com

The US FDA once again prevailed in its interpretation of the scope of three-year market exclusivity as an appeals court rejected **Otsuka Pharmaceutical Co. Ltd.**'s claim that its atypical antipsychotic *Abilify Maintena* (long-acting injectable aripiprazole) is "legally equivalent" to **Alkermes PLC**'s *Aristada* (aripiprazole lauroxil).

In an Aug. 29 opinion, the US Court of Appeals for the District of Columbia Circuit affirmed a lower court decision, deferring to FDA's view that a drug's market exclusivity applies against another product only when the two drugs share the same active moiety.

The agency determined that the active moiety in Aristada differs from that in Ability as it contains the addition of a hydroxymethly group connected by a non-ester covalent C-N bond.

Otsuka filed suit against FDA in 2015 asking the US District Court for the District of Columbia to vacate the agency's approval of Aristada and declare that FDA had wrongly denied Otsuka's exclusivity rights. It argued that Aristada metabolizes in the body into the same molecule as Abilify, and Aristada's 505 (b)(2) application relied in part on studies showing the safety and efficacy of Abilify. Thus, it said Aristada should not have been approved by FDA until the expiration of three years of exclusivity Abilify received for a clinical trial supporting a supplemental new drug application. *(Also see "Actually, It's Not About The Patient – At Least When It Comes To Product Exclusivity" - Pink Sheet, 26 Oct, 2015.)*

In July 2016, the district court granted summary judgment in favor of FDA, finding that it was not unreasonable for FDA to determine that under the Food, Drug, and Cosmetic Act (FDCA), the award of three-year exclusivity to a product blocks only subsequent applications for drugs with the same active moiety.

> A US Court of Appeals deferred to FDA's view that a drug's market exclusivity applies against another product only when the two drugs share the same active moiety.

CONGRESS DID NOT ESTABLISH 'LEGAL EQUIVALENCE'

The appeals court noted that all parties agree that the first- and second-in-time drugs must bear *some* relationship to one another but disagree about the nature of the necessary relationship. In FDA's view, marketing exclusivity applies between two drugs sharing the same active moiety.

"Otsuka, by contrast, contends that exclusivity more broadly covers any two drugs that are 'legal equivalents' – a term of Otsuka's invention that draws an equivalence between two drugs whenever one relies upon the other to receive approval," the opinion states.

The court says Otsuka appears to believe that two drugs should be considered legal equivalents if they share the same moiety; one drug relies on the other drug to receive FDA approval; or one drug relies on a drug that is itself legally equivalent to the other drug.

"Congress perhaps could have written a statute under which, if one drug relies on the safety or efficacy of a previously approved drug to obtain approval, the two drugs must be considered 'legally equivalent' for purposes of defining the previously approved drug's zone of exclusivity," the opinion states. But the statute's provisions "nowhere expressly set out any concept of legal equivalence in describing the scope of marketing exclusivity."

'TENSION' WITH COURT'S ACTAVIS RULING

Further, the court says Otsuka's notion of legal equivalence "stands in considerable tension with our decision in Actavis Elizabeth LLC v. FDA." In that 2010 ruling the court upheld FDA's understanding that a prodrug of a previously approved drug, if it has a different active moiety, can qualify as a major innovation entitled to new chemical entity status and the resulting five years of market exclusivity.

Actavis had sued FDA for awarding **Shire PLC**'s attention-deficit hyperactivity disorder drug *Vyvanse* (lisdexamfetamine) five years of market exclusivity. *(Also see "Score Five For FDA: Shire's Vyvanse Entitled To NME Exclusivity, Court Finds" - Pink Sheet, 8 Mar, 2010.)*

"If we accepted Otsuka's assertion that the scope of marketing exclusivity under the FDCA is governed by a principle of legal equivalence, that principle would apply no less to the five-year exclusivity period" granted to a new chemical entity than to the three-year periods granted to applications containing reports of new clinical investigations and supplements containing additional reports and investigations, the court said.

Shutterstock: Gutzemberg

© Informa UK Ltd 2017

The agency usually wins suits challenging its interpretation of marketing exclusivity. Last year, Otsuka struck out in trying to prevent FDA approval of generic versions of Abilify until its seven-year orphan drug exclusivity for treatment of pediatric patients with Tourette's syndrome had expired.

AstraZeneca Pharmaceuticals LP lost a similar fight to use a pediatric orphan indication for *Crestor* (rosuvastatin) to block generic competition. *(Also see "Crestor Generics To Launch After 12-Day Delay" - Pink Sheet, 20 Jul, 2016.)*

However, **Ferring Pharmaceuticals Inc.** won a suit challenging the agency's refusal to award its fixed-dose combination product *Prepopik* five years of market exclusivity as a new chemical entity. *(Also see "Ferring Wins In Combo Exclusivity Case; FDA Lacks 'Legitimate Reason' To Reject" - Pink Sheet, 12 Sep, 2016.)*

Published online September 5, 2017

Amgen v. Sandoz: Next Biosimilar Bout Begins Over State Law Claims

BRENDA SANDBURG brenda.sandburg@informa.com

Amgen Inc. and **Sandoz Inc.** are resuming their fight over whether innovator companies can obtain remedies if biosimilar sponsors do not turn over their 351(k) biologics license application (BLA) and manufacturing process information.

While the US Supreme Court unanimously ruled in Sandoz v. Amgen that innovators cannot seek an injunction under federal law if such information is not disclosed, it remanded the case to the US Court of Appeals for the Federal Circuit to decide if they could obtain damages under state law. Specifically, the appeals court must determine whether failing to disclose the data is unlawful under California's Unfair Competition Law and, if so, whether the Biologics Price Competition and Innovation Act (BPCIA) preempts any state law remedy. *(Also see "US Supreme Court Permits Earlier Biosimilar Launches; Penalty For Declining Patent Dance Uncertain" - Pink Sheet, 12 Jun, 2017.)*

The parties filed supplemental briefs with the Federal Circuit Aug. 28.

The case once again could alter the information exchange process, known as the "patent dance," for resolving patent disputes between innovators and biosimilar makers.

"The Supreme Court decided there is no federal right to enforce the patent dance. If it is decided that there is a state-based right to enforce it, that would flip the process upside down," Elaine Blais, a partner at Goodwin Procter, said in an interview. "Fifty states with 50-ish laws would cause confusion and likely change the calculus of whether parties participate in the patent dance."

IS USING DATA WITHOUT DANCING STEALING?

Amgen filed suit against Sandoz in October 2014 claiming Sandoz's application for *Zarxio* (filgrastim-sndz), a biosimilar version of *Neupogen* (filgrastim), infringed its method of use patent and violated the BPCIA by failing to provide the biosimilar application and manufacturing process information and providing early notice of intent to market the biosimilar. The complaint also claimed unfair competition for unlawful business practices under the California Business and Professions Code.

Shutterstock: Bill Perry

> "The Supreme Court decided there is no federal right to enforce the patent dance. If it is decided that there is a state-based right to enforce it, that would flip the process upside down."
> – Goodwin Procter's Elaine Blais

The US District Court for the Northern District of California ruled that Sandoz could decline to provide its application and manufacturing information and give notice of intent to launch before FDA approval. The district court also dismissed the state law claim since it found Sandoz did not violate the BPCIA.

In July 2015, a divided three-judge panel of the Federal Circuit agreed that the patent dance provisions are optional. The court said the statute provides consequences if the biosimilar sponsor

fails to turn over the information, because the reference product sponsor can immediately sue for infringement.

However, the Federal Circuit ruled that Sandoz had to wait until FDA licensure of Zarxio to notify Amgen of its commercial marketing, a holding that was reversed by the Supreme Court. The Federal Circuit also affirmed the district court's dismissal of the state law claim, ruling that the remedies in the BPCIA are exclusive remedies for an applicant's failure to comply with the information exchange process. *(Also see "Biosimilar sponsors can avoid 'patent dance' in US, but innovators win extra exclusivity" - Pink Sheet, 22 Jul, 2015.)*

During oral arguments in the case, Supreme Court justices honed in on the state law claims, raising questions as to their application. For example, Justice Neil Gorsuch asked what happens when there is a claim under state law that no one has argued is preempted. The discussion presaged the court's decision, which threw the question of preemption back to the Federal Circuit.

In its brief, Amgen contends that Sandoz stole its Neupogen data because it used the information to file a biosimilar application and then declined to go through the patent information exchange process. It is seeking restitution and compensatory and punitive damages under California's Unfair Competition Law, which is part of the Business and Professions Code.

Amgen argues that the BPCIA does not preempt state law since it does not contain an express preemption provision and does not conflict with state law claims. In addition, the relief Amgen seeks is different than the remedy provided under the BPCIA to bring a declaratory judgment action of infringement, the brief states.

The federal remedy – if it is one at all – to bring a declaratory judgment action "does not preempt state law claims because it does not remedy the competitive, but unlawful, advantage given to Sandoz by not complying with the BPCIA disclosure requirement. Nor does it remedy Sandoz's 'wrongful act' in converting Amgen's license for Neupogen without Amgen's authorization or permission and without satisfying the mandatory provisions" of the statute, Amgen says.

ARE BIOSIMILAR DISPUTES OUTSIDE STATE PURVIEW?

Sandoz argues that state law claims are preempted by the BPCIA and that the dispute is outside the purview of state law.

"Here, licensing biosimilars, policing the BPCIA's patent exchange process, and litigating federally granted patent rights are not remotely fields of traditional state regulation," Sandoz's brief states.

To the contrary, Sandoz says that only FDA has the authority to license biosimilars, patents are created and governed by federal law, federal courts have exclusive jurisdiction over patent cases, and the BPCIA's information exchange process determines the timing and scope of the federal infringement suit.

Sandoz also refutes Amgen's claim that it waived its preemption defense in the district court and in its appeal. Sandoz said it preserved the defense in telling the district court that it was not pursuing preemption at that time.

Sandoz asks the Federal Circuit to remand the case to the district court for it to address the questions on state law claims. The district court is handling the ongoing infringement lawsuit on the Neupogen patents, and Sandoz said that if necessary, the Federal Circuit could address the state law claims and any issues arising from the patent claims in one appeal after final judgment.

> A trial on the Neupogen patent infringement claims is scheduled for March 2018.

A trial on the patent infringement claims is scheduled for March 2018.

FDA approved Zarxio on March 6, 2015, at which time Sandoz provided Amgen with a second 180-day notice of its intent to market the biosimilar. It launched Zarxio on Sept. 3, 2016.

WHAT REMEDIES ARE POSSIBLE?

The Federal Circuit will determine whether Sandoz's failure to disclose its biosimilar application and manufacturing process information to Amgen is a violation of the California statute. If it is found unlawful, the question is what enforcement would entail.

"Would a California court issue an injunction saying a biosimilar sponsor may not market a product in the US until it does x, y, z?" Goodwin Procter Partner William Jay asked. He said there also is a question of whether the biosimilar sponsor will owe the reference product sponsor a lot of money if it does not follow the information exchange procedure.

Jay said that if remedies are available under state law, companies will consider what it takes to get California law applied to their case. "You might see a lot of companies try to connect a dispute to California or find another state that would produce the same result as California," he stated. Jay and Goodwin Procter's Blais represent the Biosimilars Council, which filed an amicus brief in the Supreme Court case in support of Sandoz.

The US Department of Justice filed a motion saying it is considering whether to file an amicus brief to address the preemption issue and requesting an extension of time to do so until Sept. 11. The court granted its request.

During oral arguments before the Supreme Court, Assistant to the Solicitor General Anthony Yang said the government had not taken a vetted position on preemption because the case before the court was not about that, but he said there are strong arguments that the state law claim would be preempted.

"This is a highly detailed scheme. And if states were to start to interject different means of enforcing it on a state-by-state basis, that might wreck some havoc," Yang said.

Asked if the state law would be mooted if it is preempted, Yang cited the Federal Circuit's decision that when in compliance with federal law, "you have no state law claim, because your state law claim is predicated on violating the federal law." *(Also see "FDA's Worst Case Scenario: Supreme Court Might Defer To It On Biosimilars" - Pink Sheet, 26 Apr, 2017.)*

Published online September 1, 2017

© Informa UK Ltd 2017

WHO Finalizing Guidance For Launch Of Biosimilar Prequalification Pilot

NEENA BRIZMOHUN neena.brizmohun@informa.com

Shutterstock: Thaiview

The World Health Organization is finalizing three guidelines for manufacturers that want to take part in the pilot project it is launching in October to start the prequalification of biosimilar medicines.

The pilot, which was first announced in May and was originally expected to be launched this month, will involve interested manufacturers submitting applications for the prequalification of biosimilar versions of two cancer drugs in the WHO's essential medicines list. These are rituximab for non-Hodgkin's lymphoma and chronic lymphocytic leukemia, and trastuzumab for breast cancer.

The first expression of interest covering both products will be published in October, the WHO said this week, adding that any questions can be submitted to prequalbiosimilar@who.int. The organization previously said that it planned to explore options for prequalifying insulin.

The pilot marks a step towards making some of the most expensive treatments for cancer more widely available in low- and middle-income countries, the WHO said. International procurement agencies rely on the WHO's list of prequalified medicinal products to guide bulk purchasing of medicines. Prequalification might also increase competition and further reduce the price of medicines, the organization said.

Two assessment pathways will be used in the pilot. One pathway will be for applicants with products approved by a so-called "stringent regulatory authority," i.e., a regulatory authority that is a member or an observer of the International Council for Harmonisation (ICH), or is associated with an ICH member through a legally binding mutual recognition agreement. The other pathway will be for applicants with products that were approved by other national regulatory authorities.

The WHO is currently finalizing the following three guidance documents that will be used to support the pilot:

- WHO pilot procedure for prequalification of similar biotherapeutic products;
- WHO guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products approved by stringent regulatory authorities; and
- WHO guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products – preparation of product dossiers in common technical document format.

From the editors of Scrip Regulatory Affairs. Published online September 1, 2017

Shanghai's Tough Proposals For Medical Sales Reps Draw Ire

BRIAN YANG brian.yang@informa.com

Shutterstock: hfzimages

The days when pharma sales reps could stream into hospitals and freely chat up with physicians may be ending. In addition to radical registration requirements for reps, a new rule is set to restrict interactions of sales reps with physicians in Shanghai, China's third largest pharma market.

The total number of medical sales in China is estimated to be roughly one million, notes the China Pharmaceutical Enterprise Management Association. Early this year, Chinese authorities proposed registering all medical sales reps in China, and on August 22, Shanghai took the lead becoming the first province releasing draft guidance in the area.

PHARMA SALES REGISTRY PROPOSAL

Medical sales reps represent pharma manufacturers to convey medical information, communicate with physicians and provide

feedback, said the Shanghai FDA in its proposal. The rules also apply to medical sales reps working for distributors of imported drugs and commercial staff working for companies under the marketing authorization holder (MAH) mechanism.

"Pharma sales reps are responsible for academic promotion and planning, convey information and help proper drug use, collect and provide feedback on clinical use and adverse events," noted the proposal, which rules out pharma product selling as a responsibility.

Shanghai has set up an online registry for sales reps to register. And doing so would require providing personal information including an ID, education level, phone number and years of experience, as well as company information such as the legal representative's names. All information except the ID and phone numbers will be publicly available.

Companies should strengthen legal and professional training, and punish sales reps who violate the laws/ rules or severely lack trust; such punishment should be registered with the registry, the proposal adds.

If a sales rep has bad credits, he or she will be taken off the registration, and if there are over five sales reps who have bad credits within a year, the registration for the whole company will be deleted. And upon deletion, no re-registration is allowed within two years, proposed the Shanghai FDA.

The companies have 60 work days after the rule officially takes effect to complete registering their pharma sales reps.

The draft proposal is open for comments until Sept.30. (Draft Shanghai Medical Reps Registration Management Methods – Chinese language)

PHYSICIAN VISITS RESTRICTIONS

In addition to the pharma sales reps registry proposal, Shanghai Health and Family Planning Commission on Aug. 17 released a new set of rules. The circular, titled Opinions on Strengthening Crackdowns on Pharmaceuticals Kickbacks, is among the latest efforts to tighten the grips on pharma's commercial activities (Opinions on Strengthening Pharma Kickbacks – Chinese language).

The authority requires medical sales reps to only visit hospitals at a pre-booked time and location and with pre-arranged physicians, and a record of the visit is mandated to be kept.

Meanwhile, hospital management are required to increase in-hospital patrols, strengthen monitoring, and order medical reps who meet physicians outside the pre-set time and location to leave the premises.

Shanghai has set up an online registry for sales reps, with much of the information publicly available.

VIOLATION OF LAW?

Medical sales is a profession categorized as a business activity by China's Labor Law, and sales reps should be allowed to freely conducted their activities without the restrictions of time and location, argued Shanghai-based pharma industry commentator with the pen name "Dr 2".

In an article posted on Wechat, China's social messaging platform, he said the restrictions highlight policy makers' failure to recognize medical sales' legal rights to conduct academic promotion, and are a signal of embedded prejudice deeming sales reps' hospital visits as "giving kickbacks to physicians".

"It's a laymen's policy that tries to prohibit eating because of potential choking hazard," said Dr. 2. As per China's Labor Law, medial sales can promote information to any physician, and not just pre-arranged physicians, he added.

If just a few physicians can meet sales reps, what about other physicians who have the same rights to the information, he asked.

Shanghai is the third largest pharma market in China, with annual sales totaling CNY15,261M in 2016, only trailing Guangdong province and Beijing.

Most importantly, Shanghai is the headquarters for many multinational drug makers operating in China and a commercial center for an increasing number of domestic drug makers.

"The local regulation is a distortion of national regulations, and it complicates the whole matter, implying pharma sales reps effectively can only promote pharma products to a limited few physicians," Dr 2 added.

Worse, the restrictions could severely limit their ability to conduct activities such as helping physicians in the proper use of pharma products, and collecting adverse events and providing feedback about clinical use.

Another commentator says there is little evidence that the new rule is going to help root out kickbacks, because such activities are usually conducted outside hospitals by people who claim to be sales reps but only promote product sales, not genuinely provide information, said Cao Kai of local magazine *China Hospital CEO* in an interview.

From the editors of PharmAsia News. Published online September 4, 2017

LET'S GET SOCIAL

We are tweeting, liking and sharing the latest industry news and insights from our global team of editors and analysts, join us!

@PharmaPinksheet

© Informa UK Ltd 2017

Turkey's Fast-Track Licensing System To Drive Local Drug Production

AHMET SEVINDIK pinkeditor@informa.com

Turkey's recent drive to promote the local production of pharmaceuticals by threatening to remove products made by multinationals from the reimbursement list has so far resulted in companies promising to produce 230 products locally within a year.

The manufacturers affected will need to change their licenses for these products from import to production within the space of a year. They will be able to use the Turkish Medicines and Medical Devices Agency's fast-track licensing system to do so.

The fast track system – under which the target licensing deadline is 150 days for high-priority products and 180 days for priority products – is expected to provide a significant incentive for companies to produce their drugs locally. Locally produced medicines for export are also to be included in the fast-track system, as are biotech products.

The government's drive for local production started in February this year when the Social Security Institution (SGK) negotiated with producers of originator products with 50% market share and at least three generic products. This was followed in March by negotiations with producers of originator products with 10% market share and two generics. Companies were told to produce these products in Turkey with local partners or face exclusion from the reimbursement list.

The fast-track procedure was introduced in 2012. Following a poor performance initially, 80% of applications in the high-priority category are now concluded within the target 150 days, Hakki Gursoz, head of the TMMDA, said recently. According to Gursoz, the agency is working on making this rate 100%, He also said his agency was licensing priority products within 180 days as promised.

In contrast, the 210-day target timeframe for the TMMDA's standard licensing procedure is rarely met. Last year, the median time it took to license products was 469 days (this includes the standard and fast-track procedures), and the average time it took to license products was 659 days, according to data from the Turkish trade group, the Association of Research Based Pharmaceutical Companies (AIFD).

Shutterstock: tandemich

> In some cases, companies are instructed to begin producing products in Turkey with local partners or face exclusion from the country's reimbursement list.

A big factor that delays the standard licensing process relates to the need to obtain a good manufacturing practice (GMP) certificate from the Ministry of Health. According to data from AIFD, it takes an average of 97 weeks for facility inspections to be carried out and the necessary GMP certificates to be issued due to limited human resources at the ministry.

For fast-track products, on the other hand, facility inspections for high priority and priority products and certificate issue are completed within the promised time.

Companies using the standard or fast track procedure can submit simultaneous applications for a license and a GMP certificate.

THE FAST-TRACK PROCEDURE

Regarding the fast track-procedure, products that meet certain criteria are put into either the high-priority or priority categories. These products include mostly new cancer drugs and orphan drugs that can be procured only from abroad. The products must be innovative, provide a new treatment option and meet unmet medical needs. In addition, they should be priced at levels that will reduce the amount Turkey spends on imports, and they should help healthcare management financially by reducing costs. Companies must declare the prices for their products during the application procedure and commit themselves to a certain price, which should be acceptable to the SGK.

The Ministry of Health's Working Principles and Methods of Priority Evaluation Board for Pharmaceutical Products uses a grading system to decide whether a product falls under the high priority or priority category. An original product for which there are no generics in the market gets 100 points. An original product with one licensed generic in the market (but unavailable) gets 67 points, and an original product with two licensed generics in the market (but unavailable) gets 33 points. Each criteria has a certain weighted multiplier and the process gives a final grade to each product. If it is between 75 and 100 it is high priority. If it is under 75, it is priority.

From the editors of PharmAsia News.
Published online September 4, 2017

US FDA's Drug Seizures Seen As Most Significant Aspect Of Stem Cell Crackdown

MICHAEL CIPRIANO michael.cipriano@informa.com

Shutterstock: Waldemarus

Stem cell manufacturers have rarely been subject to aggressive US FDA enforcement actions, but Commissioner Scott Gottlieb's recent announcement about a crackdown on unscrupulous companies in the regenerative medicine industry along with the seizure of product from a California facility could signal a meaningful change in how the agency targets dishonest industry players, a former FDAer says.

The Center for Biologics Evaluation and Research (CBER) has not often directed the seizure of unapproved product as it did in August with the confiscation of five vials of a live vaccinia virus vaccine at the California Stem Cell Treatment Centers in Rancho Mirage and Beverly Hills, Calif., Mark Schwartz, director at the law firm Hyman, Phempa & McNamara, told the Pink Sheet in an interview.

FDA's actions last month signal that the agency will spend a lot of energy going after bad actors – and developing a robust pathway for legitimate products to gain approval. *(Also see "Crackdown On Bad Regenerative Medicine Could Benefit Gene Therapy" - Pink Sheet, 28 Aug, 2017.)*

A product seizure "doesn't happen very often with stem cells, and with CBER generally," said Schwartz, who served as deputy director of the Office of Compliance and Biologics Quality (OCBQ) in CBER – the office in charge of compliance and enforcement for regenerative medicines – from 2012 to 2015.

> "The impression that an outside observer I think reasonably had in the past with regard to stem cell enforcement by that office, was that if you really didn't injure anybody, they weren't going to do anything to you."
> – Former FDAer Mark Schwartz

"So I am hopeful that this means that the bad actors, that over the past several years really have not seen any enforcement action from CBER, will be on the receiving end of more serious enforcement action where it is warranted."

The agency has always sent warning letters over the years to centers who marketed biological products requiring licensure that did not have approval, Schwartz said.

However, virtually no one who received those letters went down the path of pursuing an investigational new drug application (IND) and getting enough data to submit a biologics license application (BLA), according to Schwartz. Some of the players in the regenerative medicine industry would drop what they were doing on the stem cell front, but others would carry on with what they were initially doing.

"Others, seeing the environment, just concluded that the agency wasn't really going to do anything to them, because historically they hadn't really gone after people," Schwartz said.

"From my perspective, the impression that an outside observer I think reasonably had in the past with regard to stem cell enforcement by that office, was that if you really didn't injure anybody, they weren't going to do anything to you."

It is for this reason Schwartz was encouraged by the more aggressive seizure tactic, which he hopes will become more of the norm. He noted though that FDA's actions must go beyond simply Gottlieb's announcement.

"My sense is, assuming Dr. Gottlieb's statements are backed up by additional actions such as the ones that have taken place in the past week or so, that that narrative regarding enforcement will change," Schwartz said. "We have to see if it changes, but certainly the seizure in California to me was significant."

GUIDANCES COULD BENEFIT HONEST PLAYERS

Schwartz also touted Gottlieb's announcement that the agency will be issuing a series of guidances this coming fall as part of the advancing the agency's regenerative medicines regulatory framework.

Generally, entities that are engaging in stem cell procedures tend to be small facilities that make a few million dollars a year at most, Schwartz says, meaning they do not have the resources to conduct clinical trials or pay user fees. These companies could be helped by the agency outlining a more efficient process they can follow to get their products to market.

"Doing an IND and waiting a number of years to get the full quantum of safety and efficacy information in order to submit a BLA under the requirements for a traditional [Public Health Service Act section] 351 products is really very onerous for them," Schwartz said.

Published online September 6, 2017

© Informa UK Ltd 2017

FDA's NDA And BLA Approvals: Mylotarg, Tracleer

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				
Actelion	*Tracleer* (bosentan	32 mg dispersible tablet formulation of bosentan for treatment of pulmonary arterial hypertension in adults and children.	S, 5	9/5/2017
New Biologics				
Wyeth (now Pfizer)	*Mylotarg* (gemtuzumab ozogamicin)	Treatment of newly diagnosed CD33-positive acute myeloid leukemia in adults and treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and in pediatric patients 2 years and older. *(Also see "Pfizer's Mylotarg Likely To Get New Orphan, Biologics Exclusivities" - Pink Sheet, 8 Sep, 2017.)*		9/1/2017

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

Pfizer's Mylotarg Likely To Get New Orphan, Biologics Exclusivities

MICHAEL CIPRIANO michael.cipriano@informa.com

Pfizer Inc.'s 2010 withdrawal of its acute myeloid leukemia (AML) treatment *Mylotarg* (gemtuzumab ozogamicin) may have been the best thing that ever happened to the drug, at least when it comes to the product's exclusivity.

Mylotarg has already made a triumphant return to the market in scoring an unexpected pediatric indication and a watered down boxed warning compared with its initial label. *(Also see "Mylotarg Returns: US FDA Approves Pfizer's Leukemia Drug With Bonus Pediatric Indication" - Pink Sheet, 4 Sep, 2017.)* But its prospects appear to be even brighter with likely new orphan drug exclusivity, as well as 12-year biologic marketing exclusivity.

The monoclonal antibody initially scored an orphan drug designation in 1999 for the broad indication of the treatment of AML.

When Mylotarg was first approved in 2000 for the treatment of patients with CD33 positive AML in first relapse who are ages 60 and older, the drug got seven years of marketing exclusivity as part of the orphan drug designation.

Although that particular orphan drug exclusivity expired in 2007, Pfizer seems poised to move forward with another seven years of orphan drug exclusivity, since Mylotarg returned to the market with a new indication.

The US FDA gave the thumbs up to the drug Sept. 1 for the treatment of adults with newly diagnosed AML whose tumors express the CD33 antigen, as well as for the treatment of patients ages two years and older with CD33-positive AML who have experienced a relapse or who have not responded to initial treatment.

As Kurt Karst, director at Hyman, Phelps and McNamara, explained, "A designation is like a pie. You can get separate pieces of that pie approved and add separate periods of exclusivity."

The new indication "fit within the original orphan designation," for the treatment of AML, meaning the company gets the new exclusivity, Karst said.

A Pfizer spokesperson told the Pink Sheet that orphan exclusivity should be available for the new indications, but "we await notification from the agency."

It is unclear whether the exclusivity will extend beyond Mylotarg's patent life. The composition of matter patent for Mylotarg in the expired in 2015, Pfizer said, while other patents relating to Mylotarg remain in effect. Pfizer didn't return further requests for comment regarding the specifics of the patents and their dates of expiration. FDA's Orange Book lists the product as discontinued and says there are no unexpired patents for the drug remaining.

The new approval of Mylotarg comes more than seven years after Pfizer voluntarily withdrew the drug from the market after it did not demonstrate clinical benefit in confirmatory postmarketing trials, with no improvements in complete remission, disease-free survival or overall survival. Patients in the Mylotarg arm also experienced a higher rate of fatal induction toxicities, raising concerns about a safety signal. *(Also see "Pfizer Pulls Mylotarg For Safety 10 Years After Accelerated Approval" - Pink Sheet, 28 Jun, 2010.)*

Subsequent trials of Mylotarg, however, showed that fractionated doses of the drug could make its use safer. *(Also see "New data could revive Pfizer's Mylotarg " - Scrip, 13 Dec, 2011.)* It was originally approved with a recommended dose of 9 mg/m^2, but current labeling recommends dosing of 3 mg/m^2 or 6 mg/m^2, depending upon the setting.

12-YEAR BIOLOGICS EXCLUSIVITY TO BOOT?

Mylotarg also appears to be reentering the market with the 12-year biologics exclusivity.

FDA first approved the drug in 2000 as a new drug application (NDA). In 2017, however, Mylotarg was approved as a biologics license application (BLA).

This was likely due to the enactment of the Biologics Price Competition and Innovation Act (BPCIA) in 2010, which modified the definition of a biological product to include proteins, outside of any chemically synthesized polypeptide.

The Pfizer spokesperson, however, attributed the change application format to the passage of "the Biologic Licensure Application Act," stating in an email that "In 2000, MYLOTARG was reviewed as a New Drug Application (NDA) because it predated the passage of the Biologic Licensure Application Act. Biologics License Applications (BLA) were eligible for review starting in 2003. Based on today's guidance, MYLOTARG was reviewed as a BLA."

Regardless of how the change in designation originated, it's undoubtedly a good switch for Mylotarg. Under BPCIA, new biologics are eligible for 12 years of marketing exclusivity, but even if FDA decides the date of first licensure was actually the date of the initial NDA approval (and thus the biologics exclusivity has expired) Mylotarg won't ever face generic competition, it will be facing biosimilars, which are more complicated to develop.

Industry has worried that BPCIA transition requirements might create "blackout" periods for product development, where products weren't eligible to be approved as BLAs but there wasn't enough time to approve them as NDAs. *(Also see "FDA Biologic Transition Plan Creates 'Dead Zone' For Applications, Sponsors Fear" - Pink Sheet, 23 May, 2016.)*

But the Mylotarg incident illustrates that there may be some upsides the transitions as well.

Published online September 8, 2017

Shutterstock: Suwit Ngaokaew

© Informa UK Ltd 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Potential risk of gadolinium retention in the brain and other body organs in patients receiving gadolinium-based contrast agents for magnetic resonance clinical imaging procedures	Medical Imaging	Sept. 8
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

Pink Sheet

LEADERSHIP
Phil Jarvis, Mike Ward

CORPORATE SALES
John Lucas, Elissa Langer

ADVERTISING
Christopher Keeling

DESIGN
Jean Marie Smith

US
Denise Peterson
Nielsen Hobbs
Mary Jo Laffler

Europe
Eleanor Malone
Maureen Kenny
Alex Shimmings

Asia
Ian Haydock

POLICY AND REGULATORY

US
Michael Cipriano
Bowman Cox
Joanne Eglovitch
Eileen Francis
Derrick Gingery
Cathy Kelly
Brenda Sandburg
Bridget Silverman
Malcolm Spicer
Sue Sutter

Europe
Neena Brizmohun
Ian Schofield
Vibha Sharma

COMMERCIAL

US
Joseph Haas
Emily Hayes
Mandy Jackson
Jessica Merrill

Europe
Lubna Ahmed
Francesca Bruce
Peter Charlish
John Davis
Lucie Ellis
Kevin Grogan
John Hodgson
Ian Schofield
Jo Shorthouse
Sten Stovall

Asia
Anju Ghangurde
Jung Won Shin
Brian Yang
Ying Huang

EDITORIAL OFFICE
52 Vanderbilt Avenue, 11th Floor
New York, NY 10017
phone 240-221-4500, fax 240-221-2561

CUSTOMER CARE
1-888-670-8900 or 1-908-547-2200
fax 646-666-9878
clientservices@pharmamedtechbi.com

© 2017 Informa Business Intelligence, Inc., an Informa company. All rights reserved.
No part of this publication may be reproduced in any form or incorporated into any information retrieval system without the written permission of the copyright owner.

Clinical & Research
Excellence Awards | 2018
Pharma intelligence | informa

Entries are open!

Clinical & Research Excellence Awards

Join us as we honor and applaud those in Clinical R&D who, through their passion and unwavering commitment, make human lives better.

2018

www.clinicalresearchexcellence.com

25 April | Boston Harbor Hotel, Boston

General Enquiries:

Jo Kirkpatrick | Tel: +44 (0) 20 7017 7180 | Email: jo.kirkpatrick@informa.com

Sponsorship and Table Booking Enquiries:

Chris Keeling | Tel: +44 (0) 20 3377 3183 | Mobile: +44 (0) 7917 647 859
Email: christopher.keeling@informa.com