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Quest For 'It Factor' Continues In Competition For EMA After Brexit

MAUREEN KENNY maureen.kenny@informa.com

In its campaign to host the European Medicines Agency after Brexit, Dublin is highlighting the fact that it is close to London – both geographically and culturally.

According to Dublin's EMA campaign, Ireland's capital city is a great place to live, and the cultural similarities between the two cities would make it easier for existing EMA staff to move there than to one of the other cities that, like Dublin, are keen to host the agency after the UK leaves the EU. Importantly, though, if existing EMA staff wished to stay in London and commute, they could do so, given the fact that Dublin is so close to London geographically.

Ireland says there are many reasons Dublin should host the EMA. However, it will be hoping its "geographical and cultural proximity" to London will provide the "it factor" that will put the country ahead of its competitors.

> Ireland is one of a growing number of European countries that have announced their candidacy for the EMA.

Ireland is one of a growing number of EU member states that have announced their candidacy for the EMA, although formal bids cannot be made until the official hosting criteria are released. *(Also see "Race Hots Up For EMA After Brexit" - Pink Sheet, 21 Apr, 2017.)* This is expected to happen in June and there is pressure for a decision on a new host country and city to be made by autumn. *(Also see "Suspense Continues Over Formal EMA Hosting Criteria, October Decision On New Home Likely" - Pink Sheet, 2 May, 2017.)* Competition is already fierce.

"One of the biggest concerns in moving the EMA will be the transition for staff with families and close ties to London," says Lorraine Nolan, the chief executive of Ireland's Healthcare Products Regulatory Authority. "Geographically, a move to Dublin will allow employees to make the transition easier due to the proximity to London (through commuting or easy visits) in the first instance. It will ensure business continuity and staff retention," Nolan said in a statement to the *Pink Sheet*.

"Culturally, the similarities between Dublin and London (for example, language, customs etc) will also make the transition much smoother and the culture shock will not be as severe as a move to other countries in Europe."

Commuting between Dublin and London is "a very realistic option… even on a longer-term basis," says the recently issued 32-page Dublin campaign brochure. "[Dublin's] proximity to London can play a large part in the sustainability of the EMA in its current format. Dublin and London are both in the same (GMT) time zone. Following the UK's departure from the EU, Ire-

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land will be the only country within the network with English as its primary language. Dublin offers excellent air connectivity with other EU capitals and the rest of the world. The Dublin-London air route is one the busiest international routes in the world, with up to 370 flights per week and a flight time of just over one hour, enabling existing staff of the EMA to commute should they wish."

Irish health minister Simon Harris has been carrying out some heavy-duty lobbying to promote the Dublin bid. The Irish campaign earlier this month tweeted that Harris had met his counterparts from Romania, Spain, Greece, Portugal, Cyprus, Malta and Italy to discuss Dublin's candidacy.

THE COMPETITION

Lille is another confirmed bidder. With its high-speed, 1 hour 22 minute Eurostar rail link to London, the northern French city also fits the "commutable from London" bill. The Danish capital Copenhagen highlights among other things the fact that it has canals clean enough to swim in, the Barcelona bid team has highlighted the general desirability of the Spanish city "as a place to work, live and play", and the Netherlands says a move there – to Amsterdam specifically – would "enable the EMA's staff to move easily and settle down quickly within an internationally oriented society."

Sweden, like Ireland, recently launched a website promoting its bid (see www.ematosweden.eu and www.emadublin.ie respectively). The "capital of Scandinavia" wants the EMA to relocate to Stockholm, where "modernity meets tranquility" and which has "trend-setting restaurants and vibrant nightclubs next to [an] idyllic archipelago".

Countries that are particularly active in the EU medicines regulatory network are highlighting the fact. Sweden notes that its Medical Products Agency is "currently one of the most active partners of the EMA, second only to the UK when it comes to contributions." The Netherland says its Medicines Evaluation Board is "one of the most prominent national medicines regulators in Europe."

DELEGATIONS TO EMA

As of early May, representatives of governments and/or municipalities of 21 member states had approached the EMA and declared an interest in hosting the agency. The EMA has received delegations from around three-quarters of these, the agency told the *Pink Sheet*.

> The delegations from Portugal, Greece and Spain held informal meetings with nationals from their respective countries during their visits to the EMA.

The 21 countries are: Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Greece, Ireland, Finland, France, Germany, Hungary, Italy, Malta, Netherlands, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden.

The bid team for Barcelona made a point of highlighting the fact that the Spanish delegation that visited the EMA in early May held a question and answer session with the Spanish nationals who work at the agency. Two other delegations have held similar meetings. "Visiting delegations can request informal meetings with nationals from their respective countries, and some of them have done so. So far, such meetings took place at the request of delegations from Portugal, Greece and Spain," the EMA said.

Spain also made much of the fact that if Barcelona were chosen as the new host city for the EMA, it would straight away start providing free Spanish language lessons to all agency staff and their families. Asked whether other delegations had made a similar offer, the EMA said that while prior linguistic training for staff would be "very important" to facilitate a smooth transition to the new location, it was up to each remaining member state to decide and announce what they would include in their bid to the European Council.

It will be well after the decision on the future seat of the agency is taken before the EMA knows how many staff will move with it. The *Pink Sheet* asked the agency whether it knew which cities were currently the most popular among its staff members, who numbered 897 as of December 2016, according to the EMA's newly released 2016 annual report. The EMA said it had run "a number of pulse surveys to take the temperature of staff and estimate their likelihood to move with the Agency" but the results were not validated and had not been published. Nor had they been communicated to member states.

Lobbying is set to intensify as bidding cities vie for the position of strongest candidate. At the end of the day, though, other factors entirely may come into play that could thwart even the strongest-looking bid. Will the fact that it is not in the Eurozone count against Denmark, for example? Or will the fact that the current head of the EMA is Italian make it difficult for Milan to be awarded the agency?

The EMA will continue to monitor the impact of eventual staff losses on its operations and look into ways to support staff retention. It is keenly aware that a successful relocation is key to its being able to continue to meet its public health commitments.

Industry broadly speaking doesn't mind where the EMA goes as long as there's a vigorous focus in the selection process on "retaining a highly competent staff component" and the new location meets what it says are the "very essential criteria" needed to ensure as seamless a transition as possible and the continued smooth operation of the agency. As the EMA itself stresses, these include world class connectivity, excellent transport links, an appropriate building and a hotel network large enough to accommodate the wide range of experts and professionals who engage with the EMA every year. *(Also see "Suspense Continues Over Formal EMA Hosting Criteria, October Decision On New Home Likely" - Pink Sheet, 2 May, 2017.)*

These are difficult times for many of those who work at the EMA. It's not surprising to hear the Netherlands say that "uncertainty about the move is already affecting the work and family life" of the EMA's nearly 900 staff. The sooner a location is chosen the better for all concerned.

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Brazil's New Patent Agreement Is "Real and Concrete Threat" To IP

FRANCESCA BRUCE francesca.bruce@informa.com

A joint ordinance signed recently by Brazil's medicines regulator, ANVISA, and the National Institute of Industrial Property, INPI, could be bad news for pharmaceutical companies filing patents in Brazil. The ordinance creates an inter-agency policy group that will harmonize the interpretation of patent statute, and Brazil-based lawyer Otto Licks, founder and partner at Licks Attorneys, believes the move presents a "real and concrete threat" to Brazil's patent system.

The ordinance was aimed at ending 16 years of wrangling between the two bodies about their roles in the patent application process, which over many years has led to delays in the granting of patents *(Also see "Brazil Patent Agreement Hopes To Increase Flow Of Generics To Market" - Pink Sheet, 19 Apr, 2017.)* According to a statement from ANVISA, the agreement with INPI will speed up the analysis of patent applications and help get new generic medicines to market.

> "We can expect these new criteria to be anti-patent oriented."

Many problems have been down to the contentious issue of prior approval (also known as prior consent), which gave ANVISA the authority to play a part in the patent application examination process (*see box for information on prior approval*). ANVISA has often used the mechanism to veto patents, most recently the agency said it would oppose a patent application from Gilead Sciences Inc. for sofosbuvir, the active ingredient of its hepatitis C drug Sovaldi *(Also see "Brazil Prepares To Make Its Own Sovaldi As Regulator Opposes Patent Application" - Pink Sheet, 7 Apr, 2017.)* Pharmaceutical companies have complained that the mechanism leads to delays and confusion, particularly when INPI disagrees with ANVISA. The matter has gone to federal courts and there have been several rulings that ANVISA should not be allowed to examine patentability requirements.

Now, the ordinance stipulates that INPI will take responsibility for analyzing patentability, while ANVISA's role in the patent process will be to analyze public health matters, for example whether the substance under review is banned in Brazil. ANVISA will also give to INPI an opinion on patentability aspects, such as novelty and inventive step, if the product in question is of strategic value to Brazil's public health system. The ordinance says INPI will have the final say.

ANTI-PATENT ORIENTATION

However, Licks believes the new ordinance will create problems for innovator companies and that ANVISA will maintain a strong influence over the patent application process. He is concerned de-

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PRIOR APPROVAL

Prior approval goes back to 2001, when updates to Brazil's 1996 patent statute came into force giving ANVISA rights to review a patent application relating to a medicinal process or product on the grounds of public health. The aim was to ensure that generic medicines did not face undue delays to market entry. However, the mechanism proved problematic and confusing for pharmaceutical companies as ANVISA became more involved in the patent application examination process. What exactly ANVISA's role in the process should be and whether it should have one at all has been in dispute for 16 years. Already INPI faced big application backlogs and ANVISA's role in the process only made these worse *(Also see "Companies challenge Brazilian regulator's right to veto patents" - Scrip, 16 Jan, 2015.)* According to lawyer Otto Licks, ANVISA takes around three years to decide on prior approval, which makes the process much longer. INPI has a backlog of 261,000 patent applications, 31,020 of which were filed in 2016. In 2016 INPI granted 4,771 applications, just 15% of the number filed, says Licks. According to public health advocates, prior approval is perfectly legal under Brazilian law and allowed for under the TRIPS agreement (the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights) flexibilities for developing countries.

cision making regarding patent approvals will now be based on how a newly-created Inter-agency Policy Group will interpret patentability, rather than procedures and criteria outlined in Brazil's patent statute. "We can expect these new criteria to be anti-patent oriented," he told the *Pink Sheet* in an interview. According to Licks, ANVISA has shown through its analysis of patentability requirements over the past 15 years that it does not defer to patent statute.

This Inter-agency Policy Group will be made up of representatives from both ANVISA and INPI and will establish new criteria for analyzing patentability. Whenever the group issues a new interpretation of patentability, INPI will have to comply with it and update its examination guidelines, says Licks. His concern is that ANVISA has more political power than INPI and that it will have greater influence over the policy group when it comes to the analysis of patentability requirements. He also believes that the ordinance contains provisions that will allow ANVISA to pressure INPI to agree with it.

There are several areas where ANVISA has shown a tougher interpretation of patentability claims, says Licks, for example, those relating to chemical and pharmaceutical processes, new uses, polymorphs and co-crystals and enantiomers. "In these areas, the agency will try, and most likely succeed in its attempt, to overrule INPI's established criteria," says Licks.

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Furthermore, Licks doubts that the agreement will do little to speed up the granting of patent applications. Under the ordinance, ANVISA will review patentability first, before INPI and applications will stay with the medicines regulator until it has concluded its analysis. During this time INPI cannot proceed with its examination. Licks points out that this will lead to delays as ANVISA can take up to three years to do its analysis. As a result, it takes an average of 11 years to grant or reject a patent application, says Licks.

The ordinance comes into effect on June15.

From the editors of Scrip Regulatory Affairs. Published online May 12, 2017

Safety Events For Accelerated Approval Drugs Highlighted As Expansion Looms

MICHAEL CIPRIANO michael.cipriano@informa.com

Amid the ongoing expansion of the US FDA's accelerated approval program via the 21st Century Cures Act, safety events for drugs approved through the pathway have been prominent throughout the twenty-first century according to a study.

Postmarketing events were statistically significantly more frequent among novel drugs and biologics approved between 2001 and 2010 that garnered accelerated approval, corresponding author Joseph Ross of the Yale University School of Medicine writes in a JAMA study published May 9, which highlights the importance of continually monitoring the safety of these products throughout their life cycle.

"Collaboration between the FDA and other stakeholders is necessary to develop and maintain an effective system for detecting postmarketing safety events," the study says.

The study examined the 222 novel drugs and biologics approved by FDA between 2001 and 2010, 28 of which received accelerated approval. According to the authors, 39.3% of products with accelerated approval experienced a postmarketing safety event at 10 years following approval, compared with just 29.7% of those that did not receive accelerated approval.

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Safety events were measured by the issuance of safety communications, boxed warnings added in the postmarketing period and product withdrawals.

In total, there were 123 postmarketing safety events – including 59 safety communications, 61 boxed warnings and three product withdrawals – impacting 71 new therapeutics, or roughly one-third approved during that time frame. The median time from approval to the first postmarket safety event was 4.2 years.

ILL-TIMED FINDINGS?

The findings come at a time with FDA is in the midst of implementing its regenerative medicines provision as directed by the 21st Century Cures Act, which includes allowing the agency to grant accelerated approval for regenerative therapeutic products.

The law creates a Regenerative Medicine Advanced Therapy (RMAT) designation, which allows for early and frequent communication between sponsors and FDA. A similar concept to the breakthrough therapy designation, the RMAT designation has the goal of helping to reduce overall product development times, Center for

Biologics Evaluation and Research (CBER) Director Peter Marks has said. *(Also see "US FDA First's RMAT Designation: Humacyte Got A 'Quick Response'" - Pink Sheet, 26 Mar, 2017.)* Discussions with FDA may include whether accelerated approval may be appropriate for the designated product based on surrogate endpoints.

An FDA spokeswoman tells the Pink Sheet that the agency does not comment on specific studies, "but evaluates them as part of the body of evidence to further our understanding about a particular issue and assist in our mission to protect public health." She added that FDA is reviewing the findings of the paper.

OTHER RESULTS

The study also found postmarket safety events were statistically significantly more frequent among biologics, products indicated for the treatment of psychiatric disease and those with near-regulatory deadline approval.

Near-regulatory deadline approvals included products "approved within 60 days of the PDUFA deadline based on the submission and goal review dates." Those at least 60 days before the deadline, any time after the deadline or after multiple review cycles were not counted as near-regulatory deadline approvals. Roughly 39% of approved near-regulatory deadline products during the time frame experienced a postmarking event within 10 years, compared 28.7% of other approvals.

Additionally, 36.1% of approved biologics approved experienced a postmarketing safety event within 10 years, compared with just 29.7% of drugs. Meanwhile, 60% of psychiatry drugs experienced a postmarketing event within 10 years, with autoimmune, musculoskeletal and dermatology products being the next highest therapeutic area with 42.5% of its products.

Orphan products and those that received priority review, however, were not found to have a statistically significant relationship with postmarketing safety events.

"Our finding that therapeutics approved after the shortest regulatory review times were associated with a lower frequency of postmarket safety events conversely raises the possibility that some approval packages provide clearer evidence of safety, allowing for more rapid regulatory approval," the study says.

"The study also found postmarket safety events were statistically significantly more frequent among biologics, products indicated for the treatment of psychiatric disease and those with near-regulatory deadline approval.

A previous JAMA study offered caution about products approved through any of the expedited approval pathways. Trials for these drugs tend to involve less patients, which leaves more unanswered questions about their safety in the postapproval phase. *(Also see "Not So Fast On Expedited Approvals, Drug Safety Researchers Caution" - Pink Sheet, 19 Nov, 2013.)*

FDA officials, however, believe there will be fewer safety-related product withdrawals in the future thanks to improvements in safety assessment and greater mechanistic understanding of common adverse events. *(Also see "Not So Fast On Expedited Approvals, Drug Safety Researchers Caution" - Pink Sheet, 19 Nov, 2013.)* The agency has historically demonstrated a tendency waiting for a longer period of time before withdrawing drugs that were first in their pharmacologic class or that represented a therapeutic advance in an existing class, compared with "me too" drugs. *(Also see "Medical Advances Get More Chances When Safety Issues Arise" - Pink Sheet, 19 Nov, 2013.)*

However, A US Government Accountability Office (GAO) report released in January was critical of FDA's postmarket oversight of drugs approved through an expedited pathway, finding that its data on safety issues for these drugs is unreliable and difficult to access. *(Also see "Do Drugs Given Expedited Approval Have More Safety Risks? GAO Says US FDA Can't Tell" - Pink Sheet, 21 Jan, 2016.)*

ROLE FOR PREMARKET DATA SHARING

In addition to touting the Sentinel Initiative as a good first step, the most recent JAMA study suggests that "sharing of premarket clinical trial data may also bolster such efforts to more promptly identify postmarketing safety events by providing patient-level data to independent researchers for more safety and analysis."

FDA has long been a proponent of sponsors sharing their data. Data sharing can help sponsors to fill information gaps in the pre- and postmarket development phases, including help to informing medical product development and adverse event susceptibility. It can also help FDA address issues in regulatory science and public health, says Ameeta Parekh, senior advisor for scientific collaborations in the Center for Drug Evaluation and Research's (CDER) Office of Translational Sciences.

"Collectively, there is strength in numbers," Parekh said May 4 at the Food and Drug Law Institute's (FDLI) annual conference.

Parekh, however, noted that while FDA can be a cheerleader for data sharing, the data ultimately belongs to the sponsors, and that the agency cannot force the issue.

Vikram Sinha, associate vice president and head of quantitative pharmacology and pharmacometrics at **Merck & Co. Inc.**, said that many scientists get very excited about the prospect of sharing data, especially patient-level data, and that it is a common practice in industry through venues such as public meetings and publications.

"Anytime there is an opportunity to share data, you will see all the scientists raise their hands and jump immediately and say, 'We must do this. We must share. We must join this initiative,'" Sinha, also a former director of the Division of Pharmacometrics in FDA's Office of Clinical Phar-

macology, said at the FDLI conference. "And we will advance our knowledge base in a particular area tremendously.

"I think without actual data sharing, progress is going to be very limited," he added. "And it is going to be very limited in the areas where we have tremendous unmet need," such as the fields of Alzheimer's and Parkinson's.

Although the benefits of data sharing usually outweigh the risks, Sinha says, the risks still do exist. One of the main concerns is the issue of intellectual property.

"By sharing certain amounts of data, are we unintentionally providing some advantage to some other competitor?" Sinha asked rhetorically.

Sinha went on to praise FDA's affirmation of data sharing, saying that it makes a big difference in industry's decision to practice it.

Paul Hastings LLP partner Behnam Dayanim concurred with the importance of the endorsements from governmental agencies. He also suggested at the FDLI conference that policy makers enshrine in data sharing rules the use of third parties "who can be trusted both to curate the data and ensure the data is of good quality, and also maintain compliance with privacy and security obligations."

FDA released draft guidance in May 2016 outlining its recommendations for what elements sponsors should consider when using an electronic health record system to collect and transmit clinical trial data, which can be key to data sharing. *(Also see "FDA Recommends HHS-Certified Electronic Health Records For Clinical Trials" - Pink Sheet, 24 May, 2016.)*

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On The Rise In The EU: New Drug Applications, Conditional Approval Recommendations

IAN SCHOFIELD ian.schofield@informa.com

The number of medicinal products submitted to the European Medicines Agency for an initial evaluation continued on an upward trend in 2016, reaching a total of 114 compared with 111 in 2015 and 100 in 2014 respectively.

At the same time, the number of positive approval recommendations by the EMA's scientific committee, the CHMP, at 81, declined from the five-year high of 93 seen in 2015, but was in line with the figures from the two previous years, according to data from the EMA's annual report for 2016.

The breakdown of initial applications – into orphans/non-orphans, biosimilars, generics, pediatric use drugs, and so on – has remained fairly constant over the past three years, with non-orphan medicines consistently topping the charts to reach 40 in 2016. Orphan applications have also been on the up since 2013, rising from 18 in that year to 27 in 2016.

Generic/hybrid/informed consent applications matched the number of non-orphan new drugs in both 2014 and 2015 (at 37 and 36 respectively), but fell back last year to 31. Biosimilar medicines performed well, with applications rising from just one in 2013 to 14 in 2016.

But still languishing at the bottom of the chart are Article 58 applications for CHMP opinions on drugs meant for use outside the EU (i.e., in developing countries) and those for old medicines formulated for use in children (pediatric-use marketing authorization/PUMA).

The 2012 to 2015 period showed just one Article 58 application per year, and zero in 2016, while just three PUMAs were filed over the five-year period – one each in 2013, 2015 and 2016.

The EMA is looking into how it can encourage more applications under the Article 58 procedure, particularly for drugs intended for use in countries in sub-Saharan Africa.

European applications for drug approval are still on an upward trajectory

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Of the drugs whose evaluation was completed by the CHMP in 2016, 81 were given a positive opinion, while 16 were withdrawn before an opinion was delivered, generally because the data were not sufficient to support a marketing authorization (MA).

NO NEGATIVE OPINIONS

For the first time in the five-year period, the CHMP issued no negative opinions in 2016 (two products initially rejected were subsequently OKd upon re-examination). By comparison, four negative opinions were delivered in 2015, three in 2014 and five in 2013.

The EMA suggests companies should draw a lesson from the two initial rejections: "The applicants who initially received a negative opinion had not requested scientific advice," it says in the annual report. It adds that 57% of applicants who received a positive opinion on their products in 2016 had taken scientific advice.

Number of initial evaluation applications to EMA, 2012-2016

2012	2013	2014	2015	2016
96	80	100	111	114

In fact, the number of requests for scientific advice rose last year by 20% compared with 2015 to reach 582. As in the previous four years, most of the requests came from medium/large pharmaceutical companies (405 in 2016), and the rest from small and medium-sized firms (177).

The requests related mainly to products already authorized for marketing. "EMA encourages companies to seek scientific advice throughout the life cycle of their medicines," the report says. Advice on study design can relate to extensions of indication, the development of new doses and formulations, and the assessment of the drug's safety and efficacy in real life.

> "Applicants who initially received a negative opinion had not requested scientific advice" – EMA annual report

In terms of therapeutic area, anticancer drugs accounted for by far the largest proportion of scientific advice requests, at 225. There were 76 requests for products for the nervous system, 49 for systemic anti-infectives and 41 for blood and blood-forming organs.

CONDITIONAL MAS, ACCELERATED ASSESSMENTS

Of the 81 medicines that were granted a positive opinion in 2016, eight were recommended for conditional marketing authorization (CMA), where a drug can be approved early on a less complete set of clinical data than is normally required and can later gain a full MA on the basis of additional post-authorization data. *(Also see "7 Biosimilars, 2 ATMPs Among 81 Medicines That Got EMA Nod in 2016" - Pink Sheet, 18 Jan, 2017.)*

The figures for 2015 and 2014 were three and five CMAs respectively (although in the latter case three applications were withdrawn after the CHMP opinion and before a final decision on approval by the European Commission).

Last year, two drugs that had received a CMA were converted to full MA status after the manufacturers fulfilled their post-approval obligations. Since the CMA was introduced in 2006, 13 drugs out of 33 with a CMA have been converted to a full MA. The average time taken for companies to meet their obligations and gain a full MA is four years, the EMA says.

Although use of the CMA seems to be increasing, EU regulators are looking into how the process can be used more effectively. *(Also see "Pharma Showing More Interest In Conditional Approvals; Back On EU Expert Group Agenda" - Pink Sheet, 14 Mar, 2017.)*

Another evaluation tool available to the EMA is accelerated assessment, which is reserved for new drugs that address an unmet medical need. Seven new products received a positive opinion in 2016 after an accelerated assessment (as did one drug under the Article 58 procedure).

For the first time since 2012, more products were rejected (13) than were accepted (12) for accelerated assessment. "The main reasons for rejection were that either the unmet medical need was not adequately justified or the data was not sufficient to justify a major public health interest," the report says.

In 2015, 17 requests for accelerated assessment were accepted and just six rejected, while in 2014 the figures were 12 and three respectively.

Also in 2016, the CHMP adopted 59 positive recommendations on extensions of indications, five of which were deemed "significant" and qualified for an additional year of market exclusivity.

ASSESSMENT TIMES

The average times for centralized drug approval procedures have remained fairly stable over the past five years, with the CHMP assessment phase hovering around the 180-200-day mark, and the clock-stop phase varying from 131 to 187 days. The time taken for the commission to issue a decision on marketing authorization following a CHMP opinion has shown a downward trend over the period, declining from 87 days in 2012 to just 52 days in 2016 (EU rules allow the Commission 67 days for a decision).

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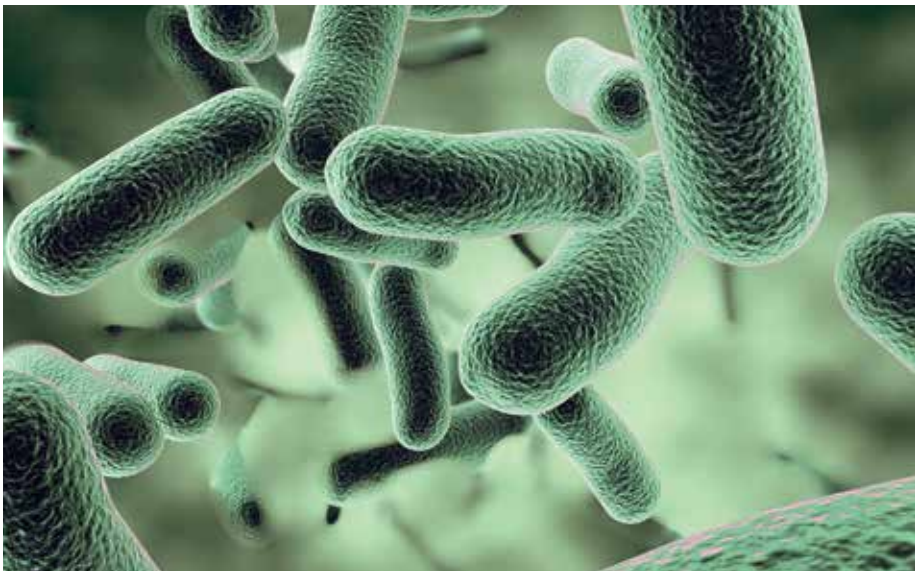
Expedited Review Pathways: Three More Breakthroughs, Third RMAT Awarded

BRIDGET SILVERMAN bridget.silverman@informa.com

The latest breakthrough therapy designation (BTD) awards from FDA illustrate the expedited review program's appeal for sponsors who are entering Phase III in areas where there is little relevant precedent to guide trial design.

Increased communication with US regulators will help advance**Synthetic Biologics Inc.**'s microbiome therapeutic, **Proteon Therapeutics Inc.**'s recombinant vasodilator, and **River Vision Development Corp.**'s (now **Horizon Pharma PLC**'s) antibody for a rare inflammatory eye disorder. (*Keep track of BTD awards and pipeline progress with the Pink Sheet FDA Performance Tracker's Breakthrough Therapy Designations chart*.)

The newest expedited review pathway, the regenerative medicine advanced therapy (RMAT) designation administered by FDA's Center for Biologics Evaluation and Research (CBER), is off to a solid start with the announcement of the third RMAT designation, for **Vericel Corp.**'s expanded autologous multicellular therapy.



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> The newest expedited review pathway, the regenerative medicine advanced therapy designation, is off to a solid start with announcement of the third RMAT designation, for Vericel's expanded autologous multicellular therapy.

VONAPANITASE GETS VOTE OF CONFIDENCE AFTER PHASE III MISS

The Phase III PATENCY-1 trial of Proteon Therapeutics' vonapanitase may have failed to meet its primary endpoint of improving primary hemodialysis vascular access outcomes, but the data from secondary endpoints earned the drug a BTD from FDA.

Vonapanitase was awarded a BTD for increasing arteriovenous fistula secondary patency and use for hemodialysis in chronic kidney disease (CKD) patients on or expected to initiate hemodialysis, Proteon announced May 10. The drug, a recombinant human type I pancreatic elastase permanent vasodilator, is given as a single administration in patients undergoing surgical creation of a radiocephalic arteriovenous fistula.

The BTD reflects the "clinically meaningful improvements" in secondary patency, or survival of the fistula without abandonment (final failure of the fistula) and use for hemodialysis, "although it did not meet the primary endpoint of improving primary patency," Proteon said. The BTD "speaks to the clinical importance of fistula survival and use for hemodialysis." PATENCY-1 found a 33% risk reduction for secondary patency over one year compared with placebo, a statistically significant result, while the risk reduction for primary unassisted patency was a non-significant 17%. *(Also see "Proteon Therapeutics Slumps On Phase III Study Miss In CKD" - Scrip, 14 Dec, 2016.)*

The ongoing Phase III trial PATENCY-2 will be the single pivotal study supporting a BLA if it reaches significance for both co-primary endpoints (secondary patency and fistula use for hemodialysis) Proteon said in its BTD announcement. PATENCY-2 is expected to produce top-line data in early 2019 and a BLA later that year.

SYNTHETIC RIBAXAMASE BECOMES THIRD MICROBIOME THERAPEUTIC WITH BTD

The breakthrough program offers FDA closer input in the clinical development of the first generation of microbiome therapeutics and will inform the agen-

cy's approach to defining regulatory pathways for the emerging field. With the award of a BTD to Synthetic Biologics' ribaxamase (SYN-004), FDA will be working with three sponsors on the design of Phase III clinical programs for agents aimed at dysbiosis in the gut associated with C. difficile infection.

Synthetic, however, is the first company to receive a BTD for prevention of primary C. difficile infection (CDI). **Rebiotix Inc.**'s RBX2660 and **Seres Therapeutics Inc.**'s SER-109 hold BTDs for patients with recurrent CDI.

CDI is the leading target for non-antibacterial therapies to be used in patients with bacterial infections. The only such agent approved, **Merck & Co. Inc.**'s *Zinplava* (bezlotoxumab), is not a microbiome therapeutic but an antibody that binds to and neutralizes C. difficile toxin B. Zinplava was approved in October 2016 to reduce recurrence of CDI in October 2016; while Zinplava did not have BTD, it had Fast Track status, which also brings greater communication with FDA, and priority review.

Synthetic's ribaxamase takes a different approach to protecting the gut microbiome of patients taking antibiotics than the Rebiotix and Seres programs. Ribaxamase is an oral enzyme that is not systemically absorbed. It degrades IV beta-lactam antibiotics within the GI tract, and by protecting the patient's native gut microbiome aims to prevent overgrowth of C. diff. The BTD candidates from Rebiotix and Seres are microbiota suspensions derived from donor feces that deliver commensal bacterial to the intestinal tract.

Synthetic's next step will be requesting a Type B multidisciplinary meeting with FDA to discuss the "overarching, high-level drug development plan and pathway to licensure for ribaxamase," the company said. The company hopes to start Phase III in the first half of 2018.

In Phase IIb, ribaxamase patients showed a 71.4% relative risk reduction in CDI rates compared with placebo patients. The trial enrolled 412 patients hospitalized with lower respiratory tract infection who were receiving IV ceftriaxone.

Synthetic Biologics is continuing to analyze exploratory endpoints in the study designed to evaluate ribaxamase's ability to prevent proliferation of antimicrobial resistant (AMR) bacterial strains. The company noted that the Phase IIb trial found that, compared to placebo, the enzyme significantly lowered incidence of new colonization by vancomycin-resistant enterococci (VRE).

> Synthetic's next step will be requesting a Type B multidisciplinary meeting with FDA on ribaxamase. It hopes to start Phase III in the first half of 2018.

Seres, in the meantime, recently disclosed Phase III plans for SER-109 in multiply recurrent CDI after a Type B meeting with FDA. SER-109 failed Phase II, but the company analyses identified dose and diagnostic issues to refine. *(Also see "Seres Argues Different Diagnostic Needed In Recurrent C. Difficile Trials" - Pink Sheet, 31 Jan, 2017.)*

The Phase III ECOSPOR III trial is expected to begin mid-2017, Seres reported May 4. The trial will enroll approximately 320 patients, both inpatients and outpatients, who have multiply recurrent CDI confirmed by C. difficile cytotoxin assays; in Phase II, Seres said, PCR testing may have identified patients who were C. diff carriers but who did not have clinical symptoms caused by C. diff cytotoxins. The Phase III ECOSPOR III trial will also use a ten-fold higher dose of SER-109 than was used in the prior study.

Rebiotix is also planning for Phase III trials of RBX2660 after completing three Phase II trials – the placebo-controlled Phase II PUNCH and Phase IIb PUNCH CD2 studies and PUNCH Open Label, which compared RBX2660 to matched historical controls. All three trials found significant benefits on CDI recurrence at 8 for the microbiota suspension.

HORIZON SEES PIVOTAL TRIAL THIS YEAR FOR NEWLY ACQUIRED TEPROTUMUMAB

Horizon anticipates starting the pivotal study for its newly acquired orphan eye disease therapy teprotumumab in the second half of 2017, the company said in its May 8 announcement of its acquisition of River Vision Development Corp. *(Also see "Horizon's Poor Primary Care Performance Overshadows River Vision Buy" - Scrip, 9 May, 2017.)*

Teprotumumab, a monoclonal antibody that inhibits insulin-like growth factor type 1 receptor (IGF-1R), holds a BTD for treatment of thyroid eye disease (TED), an autoimmune inflammatory disorder also known as Graves' orbitopathy. River Vision was formed to develop teprotumumab, which it licenses for TED from **Roche**. The product started as an oncology candidate under a Roche/Genmab collaboration. *(Also see "Roche reject recycled for ophthalmic indication" - Scrip, 13 Jun, 2013.)*

The breakthrough designation is based on a Phase II study in 88 patients with recent onset, moderate-to-severe TED. After six months, 69% of the teprotumumab patients and 20% of placebo patients met the primary response endpoint by showing reductions in both clinical activity score and protrusion of the eyeball from the socket (proptosis).

Horizon also emphasized the rapidity of the MAb's therapeutic effect, pointing to responder rates at week six, when 46% of teprotumumab patients but only 5% of placebo patients met the criteria for response.

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VERICEL'S IXMYELOCEL-T AWARDED CBER'S THIRD RMAT DESIGNATION

The Center for Biologics Evaluation and Research (CBER) expanded the use of its new regenerative medicine advanced therapy (RMAT) designation into cardiovascular disease with an RMAT award for Vericel's autologous expanded multicellular therapy ixymyelocel-T for treatment of patients with advanced heart failure due to ischemic dilated cardiomyopathy.

Ixymyelocel-T is the third product to receive an RMAT designation since the program was established by the the 21st Century Cures Act. The first known RMAT award went to Humacyte's *Humacyl* bioengineered blood vessel with long-term functional vascular patency for CKD patients being treated for end-stage renal disease (ESRD). *(Also see "US FDA First's RMAT Designation: Humacyte Got A 'Quick Response'" - Pink Sheet, 26 Mar, 2017.)* The second RMAT designation announced was for Enzyvant's tissue-based biologic therapy RVT-802 for the rare congenital immunodeficiency disease complete DiGeorge Syndrome (cDGS), which also earned a BTD. *(Also see "Keeping Track: US FDA Expands Indications For Roche Tecentriq, Lucentis, Approves Second Infliximab Biosimilar" - Pink Sheet, 23 Apr, 2017.)*

Vericel uses its fully closed cell-processing system to produce ixmyelocel-T from the patient's own bone marrow by selectively expanding populations of mesenchymal stromal cells and alternatively activated macrophages. The expanded cells, which are administered via transendocardial catheter-based injections, produce anti-inflammatory and pro-angiogenic factors involved in repair of damaged tissue.

In the placebo-controlled Phase IIb ixCELL-DCM study, end-stage heart failure patients with ischemic DCM who received the cell therapy had a statistically significant 37% reduction in the primary endpoint, a composite of all-cause deaths, CV hospitalization, and unplanned outpatient and emergency visits for acute decompensated heart failure over 12 months. *(Also see "Vericel Jumps On Positive Heart Failure Data" - Scrip, 10 Mar, 2016.)* The Phase IIb results were "primarily driven by a reduction in all cause deaths and cardiovascular hospitalizations," Vericel observed.

> Capricor intends to request BTD and/or RMAT designations for CAP-1002, its cell therapy for Duchenne muscular dystrophy patients with advanced cardiac disease.

WILL CAPRICOR'S CAP-1002 BE THE NEXT RMAT OR BTD?

Capricor intends to request BTD and/or RMAT designations for CAP-1002, its cell therapy for Duchenne muscular dystrophy (DMD) patients with advanced cardiac disease, the company said after announcing top-line data from a Phase I/II trial.

The 25-patient HOPE trial found improvement in measures of cardiac and upper limb function in DMD patients aged 12 years and older with cardiomyopathy secondary to DMD who were treated with the allogeneic cardiosphere-derived cells compared to usual care controls, Capricor announced April 25. "In HOPE, we saw potential effects in both the heart and skeletal muscle that appear quite compelling in an exploratory trial," the company said, highlighting signals of global cardiac scar reduction and increased thickening of the left ventricle during contraction.

Capricor aims to start a clinical trial of CAP-1002 in the second half of 2017. The company has submitted a meeting request to discuss development plans.

CORBUS ANABASUM DENIED BTD FOR SYSTEMIC SCLEROSIS

Corbus believes the fast-track status held by anabasum, its oral endocannabinoid-mimetic drug, will facilitate communication with FDA as the company plans a Phase III study in systemic sclerosis, even though FDA denied the company's request for a BTD.

"Corbus' existing fast-track status already grants it similar eligibility for more frequent meetings with the FDA to discuss the development plan for ananasum, as well as priority review and rolling reviews of completed sections of the NDA," the company said May 9.

Corbus is planning a single Phase III study of anabasum for treatment of diffuse cutaneous systemic sclerosis, incorporating guidance from an end-of-Phase II (EOP2) meeting with FDA. The company submitted a protocol to FDA on March 31, 2017, and anticipates starting the trial in the fourth quarter. NDA filing is projected for 2020.

The Phase III trial will enroll approximately 270 adults, who will be randomized to one of two doses of the drug or placebo for 52 weeks. The primary efficacy endpoint will be change from baseline at week 52 in modified Rodnan Skin Score (mRSS), which Corbus calls "a measure of skin thickening and a validated clinical outcome measure in systemic sclerosis."

In Phase II, anabasum patients had greater mean improvement from baseline, which was "considered medically meaningful," Corbus said. Anabasum patients also had statistically significant improvement in patient-reported skin symptoms and reduced expression of inflammation- and fibrosis-associated genes in skin biopsies.

Corbus also recently reported data from a Phase II trial of anabasum in cystic fibrosis. *(Also see "Corbus Cystic Fibrosis Data May Justify Longer, Larger Study" - Scrip, 31 Mar, 2017.)*

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India Pushing Ahead With Rare Disease Policy Plan

ANJU GHANGURDE anju.ghangurde@informa.com

India appears to have taken definitive steps towards a national rare disease policy, setting out a definition for such disorders in the country.

The definition adopted earlier this month specifies that a disease or disorder is defined as rare in India when it affects fewer than 1 in 2,500 individuals – along the lines of the definition in the EU where a disease or disorder is classified as rare when it affects less than 1 in 2,000.

"A comprehensive rare disease policy is being framed and a draft version is under consideration now," Soumya Swaminathan, secretary, department of health research, Ministry of Health And Family Welfare and director general, Indian Council of Medical Research, told the *Pink Sheet*.

India had earlier appointed a national committee of key opinion leaders (KOLs), chaired by Dr IC Verma of the Sir Ganga Ram Hospital, New Delhi, to draft a national rare disease policy. Some stakeholders including the non-profit, Organization for Rare Diseases India (ORDI), have apparently shared suggestions on relevant aspects. *(Also see "India Deliberates Orphan Rules" - Scrip, 25 May, 2016.)*

For a policy document to emerge, it's critical to have a "standardized and consistent" definition of rare disease in the Indian context, said Harsha Rajasimha, co-founder of the ORDI and co-director of the Center For Metabolic And Rare Diseases, George Mason University, US.

The US Orphan Drugs Act of 1983 has served as a model for several countries and other numerous international consortia have recently formed to help develop best practices for countries to define their own policies, he said.

"We now have a national definition for rare disease recently adopted by KOLs in India. There are multiple national and international groups brainstorming on aspects of rare disease policy. ORDI is contributing to several of them. Ultimately, we are all interested in seeing the adoption of the key elements that make a national rare disease policy," Rajasimha told the *Pink Sheet*.

Senthil Sockalingam, vice president and head, QuintilesIMS Health Institute Asia and Therapeutic Science and Strategy Unit (TSSU) Asia, QuintilesIMS, told the *Pink Sheet* that while there is a global trend towards developing a harmonized definition for rare diseases and most definitions are quite rigorous in relation to prevalence, it is important and necessary for "other criteria over and above prevalence", to also be considered and defined. He gave no immediate specifics, though.

There has been some debate on the definition of rare disease and the criteria for classification of a disease as rare/orphan in India; the Organization of Pharmaceutical Producers of India (OPPI), which represents leading multinational firms, earlier said that since a majority of patients with rare diseases come quite late for medical care, and most remain undiagnosed, the absolute number of patients suffering from a disease "should not ideally form the yardstick" for a definition.

The OPPI told the *Pink Sheet* that the earlier definition it provided worked out to 1.25 in 2,500 individuals.

"This does not change our position on rare diseases. We do see this [current definition adopted by India] as rational in the Indian context. We continue to believe that the Indian drug regulatory system needs to be predictable, timely and accountable to encourage research for orphan drugs," OPPI added.

UNDIAGNOSED PATIENTS

While experts underscore that a comprehensive rare disease policy is vital in India, they also highlight "more fundamental issues" to address in the country.

Rajasimha notes that proper and timely diagnosis is the biggest challenge facing the rare disease community and healthcare systems globally. India has an estimated 70 million patients with rare diseases, but most of them remain undiagnosed, he says.

"It still takes an average of five to seven years to diagnose a rare disease in the US or EU despite having an Orphan Drug Act, rare disease policies and resources for over 30 years now. The situation in the Indian healthcare system which is 70% rural, poses grand challenges in our ability to diagnose patients," he says.

While advanced testing methods including genomics, nanotechnology, imaging and other methods have been launched in India in the last five years, these are not really widely available.

"Some of these tests are high-throughput in the sense of being able to diagnose hundreds of diseases in a single test (e.g., a prenatal genetic test or new born screening test). We need a policy to mandate new born screening in India so we can detect and diagnose more diseases early – only then the patients with 10% of treatable rare diseases can benefit fully," he explains.

POLICY INCENTIVES

On whether India should consider laws similar to US orphan drug legislation including financial incentives, among others, for drug development and other tax benefits, to spur R&D interest in the area, QuintilesIMS' Sockalingam says that India needs a comprehensive rare disease/orphan drug policy – one that will address in totality the unique needs of the rare disease community from diagnosis, management and treatment and include the creation of registries, drug development and research, and access and affordability as well as other factors that will contribute to rare disease patients leading a better quality of life.

ORDI says that the policy needs to "most importantly" address patient issues of accessibility and affordability of diagnostics/treat-

ments. It, however, also emphasizes a holistic approach to incentivize stakeholders such as biopharmaceutical R&D organizations to encourage investment in therapies "without obvious economic returns".

"The US Orphan Drugs Act of 1983 and its amendments could serve as initial guide of major elements. The initial policy framework and budget allocation needs to be with a long-term view (say by 2030) to make rare diseases as easily diagnosable and treatable as common diseases in India," ORDI said in a note to the Government of India in March 22. *(Also see "Australia Insists Orphan Designations Will Last Only Six Months, Overrides Industry Objections" - Pink Sheet, 19 Apr, 2017.)*

OPPI too believes that the proposed policy should be "holistic" and address both diagnosis and treatment in rare disease management.

RARE DISEASE REGISTRY

Significantly, India has also launched a rare disease registry – taking key early steps to identify patients of such ailments.

"The Indian Rare Disease Registry is an effort to give Indians who are suffering from any form of a rare disease, a chance to be visible. This registry would initially be hospital or physician-based," the ICMR said.

The scope of the registry is expected to evolve over time, maturing from an outreach/community-building effort or a means for a basic understanding of patient and disease characteristics, to a supportive mechanism for research funding and attracting healthcare providers, it added.

The ICMR has called for letters of intent from investigators interested in participating in the national registry. It lists disorders such as lysosomal storage diseases, skeletal dysplasias and primary immune deficiency for consideration to begin with.

Local media reports indicated that the ICMR has also contacted patient groups managed by organizations such as the Indian RETT Syndrome Foundation, the Indian Society for Primary Immune Deficiency, the Organization of Rare Disorders India, the Hemophilia Federation of India, and the Fragile X Society, India, among others.

Rajasimha referred to how ORDI's helpline receives "a couple phone calls" every day from patients around the country.

"We have a patient registry with information about such patients and those from patient homes such as Tamahar. We launched a center of excellence for rare disease care coordination at the Indira Gandhi Institute for Child Health at Bangalore last year and had experience running a similar center at MS Ramaiah Hospital as well," he explained. Tamahar, a non-governmental organization, is engaged in the service of children with special needs.

He adds that on the agenda for next year are plans to initiate a formal system to maintain patient registries for rare diseases.

"Although we have not launched direct access to the patient registry, we have supported CROs and pharma companies with patient access." ORDI US has a collaboration with the George Mason University and received an international grant award from Sanofi Genzyme in 2016 (Patient Advocacy Leadership) along with the Rare Genomics Institute to create informational content on lysosomal storage diseases (a group of 50 plus rare diseases) to help various stakeholders and translate it into Indian languages.

TRIAL WAIVER

While a rare disease policy is work in progress, India does provide for a quicker regulatory pathway for orphan drugs.

Indian laws currently provide for a waiver of clinical trials for new drugs, which have already been approved outside India, in cases of "national emergency, extreme urgency, epidemics and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy". The trial waiver clause was recently proposed to be expanded to permit such exemption for drugs already approved in International Council for Harmonisation countries, subject to certain conditions.

Similarly, other proposals, including for early access and conditional approvals, are also reviewed and deliberated upon and appropriate decisions taken in accordance with the prevailing situation/requirement in India, Sockalingam added.

In 2014, India instructed all port officers of the Central Drugs Standard Control Organization that the issue of import permission for small quantity of drugs for rare diseases for personal use must be cleared "proactively and immediately" to ensure speedy availability of such drugs to needy patients.

"If any information other than the prescription is missing, it may be obtained post issue of the permission," a Feb. 21, 2014 order by the Drugs Controller General of India, Dr GN Singh, said. Subsequent amendments, if any, to this clause could not be immediately ascertained.

ORDI said that in the long-term, India should also perhaps look at additional options – such as conditional approvals and rolling reviews – particularly for alternative medicines such as Ayurveda, natural medicines, etc. that are unique to the Indian context but hold value for patients.

ENGAGING WITH STAKEHOLDERS

While most therapies for rare diseases have generally been developed in the US, the EU or Japan, there have been some signs of growing local research interest in the segment.

Rajasimha indicated that the ORDI is engaging with all stakeholders of rare diseases including biopharmaceutical companies to encourage and support R&D programs for orphan drugs. He cites the example of the Bangalore-based Aten Biotherapeutics (now Aten Porus Lifesciences) that is developing drugs for Niemann-Pick Type C Disorder, Pompe's Disease, and other rare disorders, while others like Sanofi Genzyme have long been making available, enzyme replacement therapies for patients in India purely via charitable access programs.

"**Shire PLC**, **Pfizer Inc.** and numerous other pharmaceutical companies are increasingly active in the Indian orphan drugs market. We are yet to see Indian biosimilars companies actively engaging with the rare diseases community – they are largely focused on manufacturing drugs for common diseases," he claimed.

Earlier this year, India's top-ranked drug firm, Sun Pharmaceutical Industries Ltd., acquired **Thallion Pharmaceuticals Inc.**, with an eye on the Canadian firm's orphan drug candidate, currently under development.

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China FDA Proposes Sweeping Reforms To Incentivize Innovation

BRIAN YANG brian.yang@informa.com

The China FDA has issued four major new policy and regulatory proposals that cover a wide range of topics related to review processes, clinical trials management, whole-process monitoring, and new incentives for innovation, including patent linkage and exclusivity periods to protect originator companies.

Many see the new policies, released May 11, as representing the most sweeping changes to date to be released by the country's national regulatory body, which could provide key new encouragement for both domestic and foreign innovative firms. They also come on top of a strong of other proposals the agency is considering to erase the "drug lag" and to make new drugs and devices available to patients at the same time as overseas.

"During my nearly two decades of industry experience, the set of proposals probably are the most drastic steps for the China FDA to take to move forward," Katherine Wang, a partner at international law firm Ropes & Gray's Shanghai office told *Pink Sheet*.

The planned changes are outlined in official Circular 55, titled "*Draft Proposals to Stimulate Innovation and Protect Innovators Rights*"

FOUR MAJOR AREAS

The proposals cover four major topics pertaining to new protections for patents and proprietary data:

Patent linkage.

New drug applicants should submit a statement of patents pertinent to their drugs, and either (i) an affidavit of non-infringement, or (ii) a notice to relevant patent holders of drugs that may infringe any patents within 20 days of the submission of an NDA.

Patent holders can file infringement litigation within 20 days of receiving the notice and notify the drug review agency (Center for Drug Evaluation, CDE). After receiving the litigation confirmation, the CDE can delay a review by a maximum of 24 months while it continues technical reviews.

During the period, the CDE can either approve or reject an NDA based on a settlement reached by the two sides or a final court ruling. If a court still hasn't issued a ruling after the waiting period, the CDE can go ahead and approve the drug.

All litigation after the market launch will be decided by court ruling.

Data exclusivity.

The CFDA said applicants can submit for clinical data protection application simultaneously. For both innovative new drugs and also pediatric or orphan drugs, the data exclusivity period would be 10 years, falling to three years for orphan/pediatric drugs with improved formulations. Innovative biologics meanwhile would have 10 years' protection and first generics 1.5 years of exclusivity.

The CDE would not approve NDAs for other same drugs during the protection period, except if the applicant can prove that they had generated their own data independently.

Improved data protection.

The Circular proposes that the CFDA would require any party involved in product inspection, reviewing, and testing (including reviewers and other government employees) to protect proprietary clinical data from disclosure to irrelevant third parties.

Establishment of an 'Orange Book'.

The planned catalog would list originators and new products and formulations, as well as generics that have cleared formal bioequivalence testing. The information would include active ingredient, formulation, specification, and marketing authorization holder, as well as the patent and monitoring time period, and exclusive data protection information.

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RECENT CFDA PLANS TO SPEED UP NEW DRUG APPROVALS

1. **March 21 –** changes to approval process so data obtained from multiregional studies can be used towards NDAs. *(Also see "Now Is The Time! Rule Changes To Smooth China New Drug Approvals?" - Pink Sheet, 21 Mar, 2017.)*

2. **March 16 -** CFDA commissioner Bi Jinquan says foreign drugs "welcome in China". *(Also see "Foreign Drugs Welcome As China Reforms Progress: CFDA Commissioner" - Pink Sheet, 15 Mar, 2017.)*

3. **March 8 -** CFDA prioritizes eCTDs, bioequivalence testing, data linkage for 2017. *(Also see "China FDA Lays Out eCTDs, Bioequivalence, Patent Linkage As Priorities" - Pink Sheet, 8 Mar, 2017.)*

'HISTORIC AND UNPRECEDENTED'

The proposed measures are "historic and unprecedented", Ropes & Gray's Wang declared. It is the first time, for instance, that the CFDA has specifically outlined data exclusivity periods for different kinds of new drugs, and proposed a period as long as 10 years to new pediatric/orphan drugs and biologics.

The planned patent linkage provisions would also make it easier for patent holders to file lawsuits against infringers, the lawyer noted.

Chan Yang, another legal expert and partner at Sidley Austin's Beijing office, cautioned however that originators may have less leeway when it comes to clinical trials approvals due to an effective Bolar-like exemption (which would not consider approval-related development work by generic firms to be patent-infringing).

Ultimately, the actual implementation of the planned changes will be key, said intellectual property lawyer Tony Chen, a partner at Jones Day. "The [patent] linkage needs to be based on revisions to both the Patent Law and Drug Administration Law," he told *Pink Sheet* in an interview.

Still, the CFDA seems to be moving forward and taking multiple steps in a positive direction, and the industry has long been seeking such incentives to protect innovations, Wang said.

The CFDA is collecting public comments on the new proposals via email (yhzcszhc@cfda.gov.cn) until June 10.

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Payer Communications Safe Harbor Should Extend To Off-Label Uses – Industry

SUE SUTTER sue.sutter@informa.com

"Payers have identical business planning needs for investigational products and investigational uses, and FDA should confirm that the same approach applies to communications in both contexts." – PhRMA

Drug manufacturer communications to payers about off-label uses of approved products should be protected from US FDA enforcement if those uses are being actively studied or undergoing regulatory review, biopharma companies say.

In comments on FDA's draft guidance on payer communications, industry groups and individual companies urge FDA to provide information exchanges about data on new indications the same safe harbor protection afforded to such communications about investigational drugs.

Payers "routinely seek information about investigational products and unapproved uses of approved products, particularly when such uses are being investigated for a potential label expansion," the Pharmaceutical Research and Manufacturers of America's (PhRMA) comments state.

"Payers have identical business planning needs for investigational products and investigational uses, and FDA should confirm that the same approach applies to communications in both contexts," the group said.

The pharmaceutical industry also requests FDA clarify the scope of the audience eligible to receive healthcare economic information (HCEI) related to an approved use and reduce the extent of disclosures that must accompany such information.

LONG-OVERDUE IMPLEMENTATION

Released in January, FDA's draft guidance describes information about the economic consequences of a drug's use that companies can share with payers, formulary committees and similar entities for approved products, the evidence needed to support such communications and disclosures that should be included. *(Also see "Industry Communications With Payors: US FDA Okays Info On Investigational Drugs" - Pink Sheet, 19 Jan, 2017.)*

The guidance also creates a new safe harbor for manufacturers to share certain types of information with payers about investigational drugs.

For the pharmaceutical industry, the guidance was a long-overdue step in FDA's implementation of Section 114 of the FDA Modernization Act of 1997. The provision allows manufacturers to share with formulary committees certain HCEI that is not in product labeling but is based on "competent and reliable scien-

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tific evidence." However, industry has long been hesitant to take advantage of Sec. 114 absent FDA guidance explaining its interpretation of the statute. *(Also see "Will FDA's View On Health Economic Claims Change With More Government-Funded Research?" - Pink Sheet, 27 Feb, 2012.)*

Drug manufacturers and payers have complained that a lack of FDA clarity on the scope of Sec. 114 is hindering the development of value-based contracting arrangements in which payment is tied to real-world outcomes. *(Also see "FDA's Off-Label Communication Changes Should Start With Payers – PhRMA" - Pink Sheet, 20 Sep, 2016.)*

The 21st Century Cures legislation enacted in December 2016 amended Sec. 114 to clarify the types of information that can be disseminated and to whom. It extended the audience to include payers and similar entities, and it changed the requirement that pharmacoeconomic information must "directly relate" to the approved indication to say that it only "relates."

EXPAND SCOPE TO INVESTIGATIONAL USES

The draft guidance describes FDA's thinking about HCEI communications to payers about approved indications but does not directly address FDA policies on information exchanges about unapproved uses of approved drugs. Instead, it references existing agency guidance on responding to unsolicited requests for unapproved uses and on good reprint practices.

However, the failure to explicitly extend the safe harbor to communications about unapproved uses of existing products is a significant concern for the pharmaceutical industry.

Merck & Co. Inc. said although the guidance provides a way for manufacturers to share relevant information to population health decision-makers before a new drug's approval, it "falls short of addressing the need to define a mechanism for pharmaceutical companies to provide information to payers on unapproved uses of approved products in advance of FDA approval of such a new use."

"The basis for sharing this type of information is the same as the rationale for communicating about unapproved products in advance of approval," Merck's comments state. "Population health decision-makers need this information in order to appropriately plan and budget because new indications for a product could significantly increase the patient population appropriate for a particular medication or vaccine."

Merck pointed to the example of its own PD-1 inhibitor *Keytruda* (pembrolizumab).

"At the beginning of 2016, Keytruda had two indications. By the end of 2016, Keytruda had received an expansion of one indication, the approval of two new indications, and the acceptance by FDA of filings for three additional indications," the company said. "A payer, for example, seeking to provide access to additional patients within the filed indications for such an important therapy would benefit from earlier knowledge of the data supporting and related to those new indications in order to be able to budget for the potential expense of a larger patient population utilizing that medication."

> Merck cites its PD-1 inhibitor Keytruda as an example where earlier communications about additional indications would have aided payer coverage.

LIMIT THE TIME PERIOD FOR COMMUNICATIONS

In a nod to FDA concerns that allowing freer communication about unapproved uses could promote off-label prescribing and eliminate the incentive for companies to get new indications added to labeling, industry commenters suggest FDA attach a timeframe to such information exchanges.

"The agency may define covered communications as those that discuss a new use that is actively being studied and for which the company intends to submit an NDA/BLA or supplemental NDA/BLA," **AbbVie Inc.**'s comments state. "Most payers would begin utilizing such information two or three years prior to approval of the new use. Thus, FDA could define this period of 'active study' as having an established plan for submitting an application or supplemental application within two to three years."

AbbVie also favors a narrow exception to First Amendment protections for certain manufacturer communications that infringe the exclusivity rights of other companies.

In separate comments, **Pfizer Inc.** and **Genentech Inc.** suggest limiting such communications to the time during which a labeling supplement for the new use is under FDA review.

"Since off-label use may be occurring during that time period, irrespective of any payer engagement, providing payers with current truthful and non-misleading data is just as likely to motivate them to take action to minimize off-label use (based on the data presented) as it is to allow off-label use," Pfizer's comments state.

CLARIFY THE AUDIENCE

Pharma manufacturers and other stakeholders also seek FDA clarity on the appropriate audience for HCEI under the guidance.

The draft document defines the audience as including "payers, formulary committees (e.g., pharmacy and therapeutics committees), drug information centers, technology assessment panels, pharmacy benefit managers, and other multidisciplinary entities that review scientific and technology assessments to make drug selection, formulary management, and/or coverage and reimbursement decisions on a population basis for health care organizations." Such entities should be constituted to consider HCEI and other types of information through a "deliberative process," the guidance states.

Although PhRMA said it agrees with the proposed definition, "we encourage FDA to clarify that the audience also includes the individual members of the entity types included in the definition." This would include individual prescribers who serve on formulary committees.

The National Pharmaceutical Council's comments ask FDA to broaden the range of organizations that can receive HCEI to include accountable care organizations, provider groups that share risk for patient costs and health, clinical practice guideline groups and value assessment bodies.

The American Pharmacists Association (APhA) also tries to make the case for expanding the scope of the HCEI audience to include pharmacists.

"Pharmacists are often the intermediary between patient and pharmacy benefit manager or payer when a coverage decision is being made," APhA's comments state. "Since pharmacists play a role in medication selection and communicate coverage changes to patients, APhA believes that any materials submitted by manufacturers to payers should be made available to pharmacists and other healthcare practitioners upon request."

REDUCE THE DISCLOSURE BURDEN

The draft guidance's proposed disclosure requirements are a frequent target for criticism in industry comments.

The guidance calls for manufacturers to include a conspicuous and prominent statement describing any material differences between the HCEI and labeling for an approved drug, and a disclosure as to studies or data sources that were omitted from the analysis and how they might have changed the conclusions. Manufacturers also should disclose potential financial or affiliation biases in connection with the HCEI distributed.

PhRMA said it generally agrees with FDA that disclosures providing appropriate context are important to ensure that communications are truthful and non-misleading for their intended audience.

"However, the full slate of required disclosures in the draft guidance would recommend that manufacturers provide payers with disclosures that provide much more information than is necessary to ensure payers have appropriate context for the communicated information and suggests a level of paternalism inconsistent with First Amendment jurisprudence," the group said. "The disclosures proposed in the draft guidance would be both unnecessary and unreasonably burdensome in many instances, particularly if required to be presented repeatedly."

Allergan PLC's comments urge FDA to "offer clear, streamlined recommendations for balanced and complete presentation of HCEI and disclosure statements that help achieve a pragmatic balance between scientific transparency and communicator/audience burden."

"Manufacturers' opportunities for communication with payers are limited in scope, number, and duration (i.e., infrequent meetings of short duration subject to calendar availability and/or invitation) and may not afford sufficient time to satisfy the disclosure recommendations as detailed in the draft guidance," Allergan said. "It may be more appropriate to provide detailed disclosures upon request."

The company urged FDA to clarify the definition of "material differences" between HCEI and the approved drug labeling that would trigger the need for required disclosures, and to provide manufacturers with multiple options for the timing and manner of presenting disclosures.

The pharmaceutical industry also wants to see the "competent and reliable scientific evidence" standard for HCEI exchanges with payers applied to medical product communications that are consistent with labeling.

Published online May 18, 2017

FDA's NDA And BLA Approvals: Jadenu Sprinkle

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				
Novartis	*Jadenu Sprinkle* (deferasirox)	Formulation of the iron overload treatment in granules providing 90 mg and 180 mg dosages for patients unable to swallow Jadenu tablets.	S, 5	5/18/2017

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

Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff

DERRICK GINGERY derrick.gingery@informa.com

Scott Gottlieb appears poised to pull drug pricing out of the shadows and make it a more visible action item for the US FDA, despite the agency's awkward position in the debate.

In his inaugural remarks to FDA staff, the new commissioner identified rising drug costs among the pending challenges for the agency. Gottlieb said that while FDA cannot directly deal with the issue, it can work to promote competition.

"Too many consumers are priced out of the medicines they need," he said during a May 15 all-hands meeting at FDA's White Oak headquarters. "Now, I know FDA doesn't play a direct role in drug pricing. But we still need to be taking meaningful steps to get more low cost alternatives to the market to increase competition and to give consumers more options. This is especially true when it comes to complex drugs and biosimilars."

Gottlieb was confirmed by the Senate on May 9 and sworn in May 11. *(Also see "Gottlieb Becomes US FDA Commissioner With Immediate Issues Pending" - Pink Sheet, 9 May, 2017.)*

Gottlieb seems intent on taking a more direct approach to the drug pricing issue, while still remaining within FDA's limited purview. He had been expected to stay away from pricing issues, even though he was a thought leader on the subject prior to becoming commissioner. *(Also see "Drug Pricing Pundit Gottlieb Likely To Stay In His Lane At FDA" - Pink Sheet, 14 Apr, 2017.)*

"Americans need us," Gottlieb said during his speech. "They need to be safe. They need to have medicines and products that work. They need to have opportunities to improve their health.

"People can't live a life of dignity if they don't have access to these opportunities – if they don't have access to the consumer protections that we provide and the tools of public health," he said. "We do what we do to serve that larger societal purpose."

A more overt stance on drug pricing, an issue that has become a political hot-button, may endanger FDA's perceived independence as primarily a science-based agency.

Many agency staff would acknowledge that drug costs are an issue for consumers. However, they have been hesitant to push the agency into the debate about solutions, in part because the agency cannot take price into account when it approves drugs. *(Also see "Could Drug Price Spikes Spur ANDA Priority Reviews?" - Pink Sheet, 28 Jan, 2016.)*

The Trump Administration's policies towards drug pricing remain somewhat opaque, but FDA activity is likely to be a central part of them.

New FDA Commissioner Scott Gottlieb speaks with agency staff following his first speech to them since taking office.

Photo credit: FDA

> "Now, I know FDA doesn't play a direct role in drug pricing. But we still need to be taking meaningful steps to get more low cost alternatives to the market..."
> – Commissioner Gottlieb

MORE TO COME TO DEAL WITH THOSE GAMING GENERIC REVIEW SYSTEM

After his pricing comments, Gottlieb highlighted the generic drug process and the lack of competition in some spaces, which has been offered as one option to force prices lower.

"We also need to take steps to make sure the generic drug process isn't being inappropriately gamed to delay competition and disadvantage consumers," Gottlieb said.

He added that there would be "much more to say on this topic in the coming weeks."

Gottlieb told Senators during the confirmation process that generic approvals can be more efficient and consistent to avoid encouraging speculators to take advantage of the system. *(Also see "Gottlieb Q&A: Sen. Murray Wants To Know About Generic Labeling Rule" - Pink Sheet, 30 Apr, 2017.)*

CLICK

Full text of Commissioner Gottlieb's speech Visit

http://bit.ly/2qSB8QT

The upcoming reauthorization of the generic drug user fee program will include an eight-month priority review pathway for first generics and some other products. *(Also see "ANDAs Can Get Priority, Eight-Month Reviews Under User Fee Deal" - Pink Sheet, 24 Sep, 2016.)*

The Senate Health, Education, Labor and Pensions Committee attached an amendment to the bill that would expand eligibility to products entering a market with three or fewer listed products. *(Also see "Generic Priority Review Expanded In Senate User Fee Bill" - Pink Sheet, 11 May, 2017.)*

OPIOIDS AMONG HIGHEST PRIORITIES

Gottlieb said FDA's "greatest immediate challenge" is opioid abuse, calling it a "public health crisis of staggering human and economic proportion."

He said opioid addiction was not a problem FDA alone could solve, but added the agency will play an important role in reducing abuse rates and giving providers the necessary tools to ensure opioids are only used in appropriate patients.

"Addressing this tragedy is going to be one of my highest initial priorities," Gottlieb said. He also promised "more forceful steps" would be forthcoming.

FDA opioid policy became a source of tension during Gottlieb's confirmation process, as it was during the confirmation of his predecessor, Robert Califf. Several Senators announced they would vote against Gottlieb out of concern he could limit opioids oversight. *(Also see "Gottlieb Closing In On Confirmation Despite Senate Concern On Opioids" - Pink Sheet, 8 May, 2017.)*

FOSTER INNOVATION WITHOUT RAISING DEVELOPMENT COSTS

Gottlieb also said FDA should ensure its regulatory processes are not hindering innovation.

He said the agency must "modernize how we do our own work to take advantage of advances that can help us better protect consumers and promote health by making the regulatory process itself more modern and efficient."

He cited the recently implemented Program Alignment reorganization of FDA's Office of Regulatory Affairs as an example. ORA inspection teams now are structured based on commodity rather than geography.


Photo credit: FDA

> "Addressing this tragedy [of opioid abuse] is going to be one of my highest initial priorities" and "more forceful steps" are forthcoming.

He also said the agency must ensure it is "regulating areas of promising new technology in ways that don't raise the cost of development or reduce innovation."

"We need to do all of these things without compromising our primary mandate to protect the public health," Gottlieb added.

Gottlieb has said that he would promote sharing best practices, such as for adopting the breakthrough therapies program, to increase consistency within the agency. *(Also see "Gottlieb Promotes 'Bottom-Up' Review To Increase FDA Efficiency, Consistency" - Pink Sheet, 6 Apr, 2017.)*

CALMING FEARS AND ADDRESSING UNCERTAINTY

As he closed the speech, Gottlieb also addressed the concern and nervousness that has been swirling within FDA and its stakeholders since Trump won the 2016 election.

Gottlieb said that staff have described the situation as "a period of some uncertainty for FDA." He responded that he viewed it as a time of promise for the agency.

"I want you to know I wouldn't have taken this job if I didn't think there was a clear and historic opportunity for us to advance FDA's mission and to help Americans realize more opportunities from science and medicine," he said. "Working together, I know that we'll seize that opportunity."

There was fear that Trump could make substantial changes to FDA practices. Center for Drug Evaluation and Research Director Janet Woodcock made a video for her employees encouraging them to instead focus on their work and mission. *(Also see "Woodcock Tries To Calm US FDA Staff Fears About Trump" - Pink Sheet, 21 Dec, 2016.)*

Those concerns may have helped inspire the agency's release of dozens of guidances and other documents prior to Trump taking office. *(Also see "FDA's Document Dump: Guidance Release Skyrockets Ahead Of Trump's Arrival" - Pink Sheet, 22 Jan, 2017.)*. Guidance output had slowed since the beginning of the Trump administration, as it does with any presidential transition, but since May 1 the agency has published 37 product-specific guidances (21 new and 16 revised) to aid development of generic drugs – an output in keeping the philosophy Gottlieb outlined in his speech.

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The Latest Furor Over Trump's Drug Pricing Plan

MICHAEL MCCAUGHAN pinkeditor@informa.com

By now you have probably read the comments that Office of Management & Budget Director Mick Mulvaney made about rebates in Medicare Part D.

As reported by the *Washington Post* (and a number of other media outlets and aggregators), Mulvaney indeed described the Part D program as a "tremendous giveaway to pharmaceutical companies" because "they no longer had to rebate like they did in Medicaid" during a panel discussion at the Stanford University LIGHT Forum. And he did indeed report having "floated" the idea to the President to "try to be a little bit heavier handed on the rebates they have to pay in order to try and drive the prices down."

Let the hyperventilating begin.

You can see why the *Post* treated those remarks as a man-bites-dog story, suggesting how surprising it is to hear Mulvaney (previously a Republican member of Congress from South Carolina) seeming to endorse a proposal pushed by liberal Democrats for the past decade.

However, as with so much about the Trump Administration's promises to act aggressively to curb prescription drug prices, there is more – or is it less? – to the story than it may seem. *(Also see "Who Speaks For The White House On Drug Prices? Industry Better Hope It Is Not Donald Trump" - Pink Sheet, 14 Mar, 2017.)*

The full context of Mulvaney's remarks are important. He was asked about drug pricing three different times – and for the most part his answers struck a very different tone, one much more in keeping with conservative approaches to limited government and support for free market competition.

When first asked about drug pricing by the session moderator, former California Governor Gray Davis, Mulvaney's response was an indictment of big government. "We are seeing the end result of government intervention in the market for the past 60 years," Mulvaney declared. It is also a result of "free-riding" by other countries: "We do pay more, but we get a lot more innovation."

He suggested a good starting point is an area where there appears to be bipartisan support: situations like those behind the controversy over **Mylan NV**'s *EpiPen. (Also see "EpiPen Pricing Got Mylan In Hot Water; Now Sanofi Is Taking Firm To Court" - Pink Sheet, 24 Apr, 2017.)*

In Europe, Mulvaney said, the price is extremely low because "there are eight manufacturers. There is one here." And, he declared, "it is nearly impossible for anyone to compete in our marketplace" because of the regulatory approach taken by FDA. So, when a manufacturer jacks up the price, he said, "the only thing we have is the bully pulpit" to try to drive the price down.

"Maybe it should be easier to get drugs approved" in the US, he said. At the very least, FDA should make drug/device generic approvals "easier." And "maybe if you get something approved in Europe, maybe it should be easier to get it approved here."

"And maybe you can let the market work. Is it slow? Yes. Does it function? Yes. Does it work in every other thing that we do every other good and service? Yes." So the answer, Mulvaney said, is to "fix the fundamental market distortions."

Shutterstock: Africa Studio

> As with so much about the Trump Administration's promises to act aggressively to curb prescription drug prices, there is more – or is it less? – to the story than it may seem.

MEDICARE CHANGES, LEGISLATIVE IDEAS ARE CONTEXT FOR COMMENTS

Another panelist, former OMB Director Peter Orszag, then jumped in to argue that it is strange to argue that "government intervention" is making US prices higher, when it is government intervention that makes prices in Europe lower. Mulvaney responded by declaring that "one of the costs that is wrapped up in what our people are paying is that they are subsidizing what other people are paying," and that the US has to do more to assure fair pricing overseas.

Orszag, who served in the Obama administration, also first raised the topic of Part D reforms, noting his frustration with his Democratic colleagues who continue to call for "price negotiation" without acknowledging that "negotiation by itself doesn't do anything." There needs to be a structure, like a formulary, in place to make negotiation effective – and that involves a trade-off of excluding medicines from the program altogether.

Gray subsequently asked Mulvaney more directly about whether the President plans to do something about drug prices, whether

there will be "something in the Senate" health care bill, or whether other legislation might be an option. "Yes, yes, yes and yes," Mulvaney replied. "We are looking at some things we can do internally, without Congress; what we might have to go to Congress to fix; what we can add to the [health care] bill."

The "we" in that sentence, Mulvaney added, starts with the "new FDA commissioner" (Scott Gottlieb) and also includes the CMS Administrator (Seema Verma) and HHS Secretary (Tom Price). Mulvaney's specific reference to the FDA commissioner first once again suggests that regulatory reform is the top focus for immediate action. *(Also see "FDA On Drug Pricing: Incremental Steps, But No Full-Frontal Assault" - Pink Sheet, 4 May, 2017.)*

And Mulvaney made very clear that the push for action comes from the top. "The President does keep coming back to this. A lot of the stuff that we deal with [in health care] is pretty esoteric, if you are not in the industry, it is hard to follow. The price of pharmaceuticals is one of those things that sort of sits out and everybody can see it."

So "the President keeps telling me again and again and again, 'What are we doing to fix this? What are we doing to fix this?'"

Only then did Mulvaney turn to Part D. Here is what he said, transcribed verbatim:

> *One of the things that hasn't been discussed today, one of the places that Peter and I may agree, when Medicare Part D was put in it, it was a tremendous give away to pharmaceutical companies, the fact that they no longer had to rebate like they did in Medicaid. So we actually floated that idea with the President: try to be a little bit heavier handed on the rebates that they have to pay in order to try and drive the prices down.*

There is the *Washington Post* story. But, he kept talking:

"We are looking at restructuring how the system is, how to bring new products to market quicker, looking at how differently to pay for the review process in order to try to get more skin in the game. We also are trying to get the states" to focus more on costs of health care services including drugs through Medicaid reforms.

That doesn't sound like immediate action on Part D, but rather focusing back on themes of competition and state flexibility. And Mulvaney's allusion to the paying for the review process echoes the call for a significant increase in user fees as part of Trump's 2018 budget proposal. *(Also see "100% User Fees For US FDA? Trump Budget Revives Important Issue For Industry – But Not This Year" - Pink Sheet, 23 Mar, 2017.)*

Mulvaney returned to the subject in Q&A, when **Acorda Therapeutics Inc.** CEO (and Biotechnology Innovation Organization Chair) Ron Cohen asked the first question, and urged the OMB director to focus on incentivizing "a system that pays for outcomes," rather than "a selective form of price control" like rebates in Part D.

Mulvaney responded by agreeing that an outcomes based approach is ideal, and stressed his concerns about the "risk of a monopsony buyer" and the "risk when we warp the market" as well as "the burdens we bear when other countries force us to subsidize" innovation.

Most reassuring of all, he added: "I don't think this administration is looking at this as the way to fix the problem is to have the government fix the price of your goods. That may create a short term benefit and a long term catastrophe. We get that."

> "I don't think this administration" believes "the way to fix the problem is to have the government fix the price of your goods. That may create a short term benefit and a long term catastrophe. We get that."
> – OMB's Mick Mulvaney

PART D OR NOT PART D?

So what did he really mean about Part D rebates?

- First, it is clear that the primary focus for Mulvaney remains squarely on regulatory reforms at FDA to encourage competition, and – secondarily – on more aggressive trade policies to promote free pricing in other countries. That should be music to the ears of most in industry – although they may prefer not to have those higher user fees if possible.
- Second, Mulvaney's small government, free-market principles are indeed anathema to the idea of setting up some new federal price negotiation/oversight authority. Don't expect the "Trump plan" to rely on those sorts of approaches.
- But third, Mulvaney also sees Medicare Part D less as a shining example of the free market at work, and more as a government intervention of the sort he generally opposes. And, to be fair, he is exactly right in describing the program as in part a windfall to industry – though the drugs that benefited most from the movement from Medicaid to Medicare as payor are long off-patent (think *Lipitor* and *Zyprexa*). *(Also see "The Part D Peak: Big Pharma's Blowout Quarter" - Pink Sheet, 1 May, 2007.)*

Mulvaney is also right in highlighting Part D rebates as an issue where there could well be grounds for bipartisan compromise. His answer was convoluted and confusing, but in context he seemed to be suggesting it as an element that might be on the table for Congress (rather than executive action), and one where Democrats like Orszag could well make common ground with Conservative deficit hawks.

In fact, it is almost impossible to imaging a bipartisan health care bill that doesn't include Part D rebates. That isn't something new – just an uncomfortable truth for biopharma companies.

From the editors of the RPM Report. Published online May 16, 2017

'Excessive Pricing' Inquiry Widens As EC's First Antitrust Price Probe Targets Aspen Pharma

IAN SCHOFIELD ian.schofield@informa.com

Pharmaceutical companies' pricing strategies have come under even closer antitrust scrutiny in the EU after Aspen Pharma became the subject of the European Commission's first inquiry into "excessive" pricing in the pharmaceutical industry.

The commission said it would be looking into whether Aspen abused a dominant market position by using the threat of product withdrawals to impose "very significant and unjustified prices increases of up to several hundred percent" on five anticancer drugs.

Margrethe Vestager, the competition commissioner, said that while companies should be rewarded for producing life-saving pharmaceuticals, "when the price of a drug suddenly goes up by several hundred percent, this is something the Commission may look at." She added that "more specifically, in this case we will be assessing whether Aspen is breaking EU competition rules by charging excessive prices for a number of medicines."

The South Africa-based Aspen is already being investigated by antitrust authorities in Italy and Spain, and this new inquiry, which the company said would involve "certain actions of Aspen Holdings and certain of its European subsidiaries," will significantly expand the scope of those inquiries.

Aspen said in a statement that it was not currently in a position to comment on the commission's probe, but it reaffirmed its "commitment to fair and open competition in markets in the European Union and around the world." Aspen, it declared, "takes compliance with competition laws very seriously and will work constructively with the European Commission in its process."

Noting that this was its first investigation into concerns about excessive pricing practices in the pharmaceutical industry," the commission said it would now carry out its in-depth investigation "as a matter of priority."

Aspen said in a statement that it was not currently in a position to comment on the commission's probe, but it reaffirmed its "commitment to fair and open competition in markets in the European Union and around the world."

The UK pharmaceutical industry body, the ABPI, distanced itself from the case, saying: "Please be aware that Aspen Pharmacare are not a member of the ABPI." Its executive director, Richard Torbett, said that the practice of price hikes on generic medicines "has had a damaging impact on trust of all pharmaceutical companies and the ABPI has repeatedly said that we do not in any way support or condone it."

Torbett added that the association was "fully supportive of recent legislation that will allow the UK Government to tackle excessive profiteering and close a loophole that has allowed large price hikes to a small number of NHS medicines." He was referring to the Health Service Medical Supplies (Costs) Act, which was passed in April and is intended to allow the government to regulate the prices of unbranded generic drugs.* *(Also see "ABPI Welcomes Amended Legislation On Curbing Excessive Unbranded Drug Prices" - Pink Sheet, 5 May, 2017.)*

FIVE ANTICANCERS IN THE FRAME

The investigation relates to Aspen's pricing of niche medicines containing chlorambucil, melphalan, mercaptopurine, tioguanine and busulfan, which are used to treat various cancers including hematologic tumors and are sold in various formulations under multiple brand names. The company acquired the drugs from **GlaxoSmithKline PLC** in 2009 after their patent protection had expired, and subsequently applied the price increases.

The commission said it had information that to allow it to impose the price rises, Aspen threatened to withdraw the medicines in question in some EU member states and actually did so in certain cases.

"Aspen's behaviour may be in breach of the EU's antitrust rules (Article 102 of the Treaty on the Functioning of the European Union (TFEU) and Article 54 of the European Economic Area (EEA) Agreement), which forbid the imposition of unfair prices or unfair trading conditions on customers," the commission noted.

It's not clear how long the investigation might take. The commission said there was no legal deadline for completing inquiries into alleged anti-competitive conduct, and that the duration of a case depended on factors like the complexity of the case, the extent to which the undertaking concerned cooperates with the commission, and the exercise of the rights of defence.

ITALY AND OTHER COUNTRIES

The investigation covers all the countries of the European Economic Area (the EU plus Iceland, Liechtenstein and Norway) apart from Italy, whose competition authority has already taken action against

Aspen: it fined the company more than €5m last year for abusing a dominant position by charging excessive prices for the anticancer products.

In that case, the competition authority, the AGCM, said in October 2016 that Aspen had "fixed unfair prices with increases up to 1,500% for life-saving and irreplaceable drugs in the treatment of oncohematological patients, especially children and elderly people."

The Italian investigation gives some insight into how the prices increases were achieved. Aspen, the sole distributor of the products, had asked the Italian medicines agency AIFA to re-categorize the drugs so that their prices would no longer be regulated by agreement and could instead be set freely by manufacturers, with the costs being borne by patients rather than the national health system.

Aspen, the sole distributor, had asked AIFA to re-categorize the drugs so that their prices could be set freely by manufacturers, with the costs borne by patients rather than the national health system.

According to law firm Van Bael & Bellis, when AIFA refused, "Aspen demanded a substantial upward revision of prices as an alternative. To reinforce its bargaining power, it caused a shortage of Cosmos drugs in the Italian pharmaceutical market by preventing their parallel import through the use of a stock/quota allocation system. It also threatened to terminate supply of the drugs to Italy if negotiations were to fail."

Using this strategy, the AGCM said, Aspen "obtained an extremely high increase in prices, ranging between 300% and 1,500% of the initial prices" applied by GSK.

The company may have used similar tactics in Spain, where the competition authority, having been alerted by the Italians, launched proceedings against Aspen in February 2017 for "possible abusive practices" consisting of refusal to supply certain pharmaceuticals "and for excessive prices," according to Spanish law firm Callol, Coca & Asociados.

And in January this year, it was reported that Aspen had imposed sharp prices rises on some of the products in the UK.

OTHER COMPANIES CONCERNED

Moreover, Aspen is not the only company to come under the excessive pricing spotlight. In December 2016, the UK Competition & Markets Authority issued its biggest fine ever (£84.2m) against Pfizer and a further fine of £5.2m against Pfizer's distributor, Flynn Pharma, for charging "excessive and unfair" prices for the generic anti-epilepsy drug, phenytoin capsules. Both companies were ordered to lower their prices. *(Also see "UK Fine For Pfizer/Flynn's 'Excessive And Unfair' Pricing Sends Clear Message To Others" - Scrip, 7 Dec, 2016.)*

In this case, Pfizer sold Flynn the rights to phenytoin capsules that had been sold under the brand name Epanutin. Flynn then "de-branded" the drugs, so they were no longer subject to price regulation, and imposed prices that were between 780% and 1,600% higher than Pfizer's previous prices.

That same month, Actavis also fell foul of the CMA, which released a "Statement of Objections" alleging the company "broke competition law by charging excessive and unfair prices" for generic hydrocortisone tablets, which are used as primary replacement therapy for people with adrenal insufficiency, a life-threatening disease *(Also see "Actavis UK's 'Excessive' Price Hikes Targeted In Latest Competition Inquiry" - Scrip, 16 Dec, 2016.)*

**This article has been updated to include information from the ABPI.*

From the editors of Scrip Regulatory Affairs. Published online May 15, 2017

FDA Aligns New Pharmaceutical Inspectorate Into Six Divisions

BOWMAN COX bowman.cox@informa.com

As part of a May 15 reorganization, US FDA has established a new pharmaceutical inspectorate in its Office of Regulatory Affairs and apportioned the inspectorate's staff among four domestic regional divisions, one foreign division and one program division.

The reorganization, called program alignment, enables the agency's field organization to specialize by type of product. Investigators will no long be inspecting a food facility one week and a drug facility the next. *(Also see "US FDA's Program Alignment: Where Should Form-483 Responses Go After May 15?" - Pink Sheet, 10 May, 2017.)*

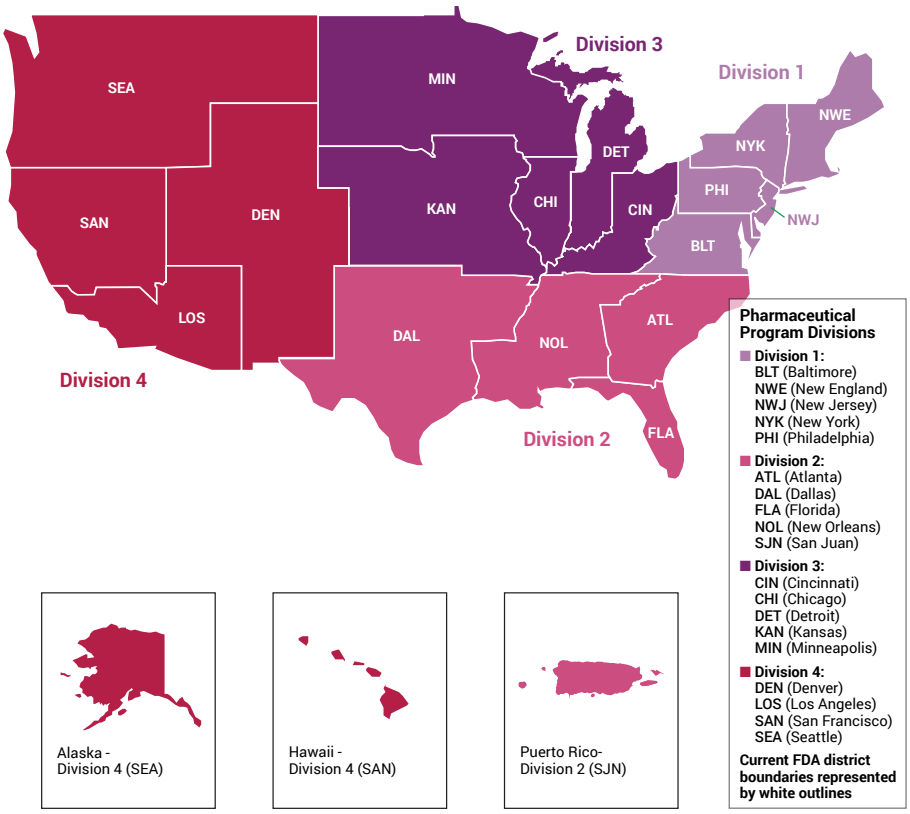
When it unveiled its intention in September 2013 to realign field staff, FDA said the goal was to keep pace with scientific innovation, global sourcing of FDA-regulated products and new programmatic mandates.

Over the past decade, legislation like the FDA Safety and Innovation Act of 2012 and the FDA Food Safety Modernization Act of 2011 has hit the field organization with divergent, commodity-specific mandates that were increasingly difficult to manage under the old structure. Now each product area has its own field organization that can specialize in commodity-specific legislative, scientific and market factors.

As before, there are 20 district directors, and they continue to manage their districts. However, instead of managing all program operations within those districts, each only manages operations for one program, and they do it for an area that also encompasses other districts.

However, there are some areas where

FDA's New Office of Pharmaceutical Quality Operations has four domestic regions



Source: FDA

ORA has opted to retain the old geographical structure: consumer complaint coordinators, state liaisons and emergency response coordinators.

ORA's new Office of Pharmaceutical Quality Operations, which corresponds to the agency's Center for Drug Evaluation and Research, is comprised of six divisions – two at headquarters offices and four based in district offices (*see map for the four regions*).

The new structure is detailed in FDA's updated ORA directory, which is part of the agency's Investigations Operations Manual. The directory gives contact information for management and staff throughout the organization.

The revised directory provides a guide to ORA that can help industry as it adjusts to the new structure and learns, for example, which FDA officials should now receive replies to Form-483 reports of inspectional observations. *(Also see "US FDA's Program Alignment: Where Should Form-483 Responses Go After May 15?" - Pink Sheet, 10 May, 2017.)*

CLICK

Visit http://bit.ly/2qwj0dQ to view FDA's new office of enforcement and import operations program divisions.

The OPQO will be directed by Alonza Cruse, who has had a lead role in the realignment as it relates to pharmaceutical inspections and has spoken about the realignment to pharmaceutical industry audiences over the past several years. *(Also see "FDA Drugs Field Staff May Be Based In Four Offices After Realignment" - Pink Sheet, 16 Jun, 2015.)*

The group's organizational chart includes these components:

- The Division of Pharmaceutical Quality Programs, which FDA told the Pink Sheet "coordinates, directs and assists the field and headquarters with domestic and international investigative activities related to pharmaceutical products." Ann Marie Montemurro is the program division director, based in Rockville, Md., at FDA's Element Building. Staff for this division were previously in the former Office of Medical Products and Tobacco Operations.
- The Division of Foreign Pharmaceutical Quality Inspections, which oversees FDA's foreign drug cadres. This program division director slot is vacant.
- Division 1. The program division director, Diana Amador Toro, is based in the New Jersey District Office.
- Division 2, program division director vacant.
- Division 3. The program division director, Art Czabaniuk, is based in the Detroit District Office.
- Division 4. The program division director, Steven Porter, is based in the Los Angeles District Office.

The updated ORA directory provides some additional specifics, including that the Division of Pharmaceutical Quality Programs, which Montemurro leads, has two branch offices. An FDA spokesman provided some additional information about these branches.

The Pharmaceutical Quality Initiatives Branch manages and coordinates implementation of new regulations and initiatives in ORA's pharmaceutical quality program. It is staffed with two pre-approval managers, a drug registration monitor and a program analyst.

The Pharmaceutical Quality Programs Branch "coordinates, directs and assists the field and headquarters with domestic and international investigative activities related to pharmaceutical products," FDA said. The directory shows that this branch is staffed by experts including investigators Thomas Arista, Sharon Thoma and Robert Tollefson, who are fixtures on the drug quality lecture circuit. The foreign inspections division has two branches, Branch 1 and Branch 2.

FDA said the four field divisions each have an investigations branch and a compliance branch, and Division 1 has an

additional investigations branch.

The agency told the Pink Sheet that program alignment should "help reduce the level of uncertainty of the pharmaceutical industry by providing timely and expected communication of our inspectional findings and facility assessments. For example, FDA is working on providing final inspection classification within 90 days of the end of an inspection." In addition, "it is likely that due to the fact that we are dedicating programmatic resources to these inspections, we may be able to accomplish them more efficiently and in less time."

IMPORT OPERATIONS ELEVATED IN FDA STRUCTURE

Also, FDA is raising its import operations organization to the level of a program.

The agency has replaced the old structure of one import district and various import operations embedded in 16 other districts. There are now five import divisions, four of which are new, and they cover all borders.

The Office of Enforcement and Import Operations (OEIO) is headed by Douglas Stearn, program director. Armando Zamora is deputy program director.

There are nine divisions under Stearn, including the five import divisions:

- The Division of Enforcement; Scott MacIntire, division director;
- The Division of Food Defense Targeting;
- The Division of Import Operations Management;
- The Division of Import Program Development, John Verbeten, division director;
- The Division of Southwest Imports, Todd Cato, division director;
- The Division of Southeast Imports, Ruth Dixon, division director;
- The Division of Northeast Imports;
- The Division of Northern Border Imports; and
- The Division of West Coast Imports.

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OTC Topicals Firm's Regulatory Problems More Than Skin Deep

MALCOLM SPICER malcolm.spicer@informa.com

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The marketer of *VenomX* and other topical OTC drugs would rather get out of the business than change following FDA's findings of good manufacturing practices problems and noncompliant claims including preventing diabetes-related amputations.

FDA's warning letter submitted on May 8 to Phillips Co., owned by Howard Phillips LLC, of Sun City, Ariz., states that the company does not appear committed to correcting the GMP, labeling and branding problems Office of Regulatory Affairs officials found following in an October 2016 at its Millerton, Okla., facility.

The letter from ORA's Dallas District states in its response to inspectors form 483 findings, Phillips "acknowledged that your 'ability to build a pharmaceutical manufacturing company has been found lacking, as shown by the FDA inspection report.'"

Phillips' website largely confirms ORA's suspicions. A page in its product catalogue, which also offers information on the company's history and plans, states: "Intellectual Property for Sale. This is, in fact, the sale of Phillips Company." The statement is followed by a list of the treatment areas targeted by the firm's 20 OTC dermatology products and descriptions of its product development and the market potential linked to its intellectual property.

The sales pitch says company president and founder Howard Phillips is "known for his pioneering work in artificial vision, has developed 20 novel products for various skin conditions that have the potential to change, according to preliminary research, the treatment standards and standard of care" in diabetic wound healing; venomous snake and spider bite treatment; bacterial skin infections, including methicillin-resistant staphylococcus aureus; tissue regeneration via adult stem cell mediation; pain control; acne; and burns.

The company also says its stem cell technology "is held as a body of trade secrets," but is not patented, though "the buyer of Phillips Company IP can seek patent protection if desired." Its product development plans stated in the catalogue include potentially renaming its *TetraStem* product for periferal neuropathy and spinal cord injury indications.

Phillips says it focuses entirely on the development of topical products because it has "the world's most effective transdermal carrier technology," which is "a dual-carrier system that can carry any active ingredient through the skin and 2.5 cm into soft tissue with a therapeutically-adequate concentration of the active ingredient."

The sales pitch concludes by stating,

"With the number of products, uses, market sectors and the sizes of the relevant markets, the possibilities cannot be overstated."

Phillips, however, is overstating the effectiveness of its *Tetracycline-ABC* and *Diabecline* brands as well as VenomX and TetraStem, ORA stated in the warning letter. Claims for the topicals render them unapproved new drugs. Tetracycline 3% is active ingredient in each of the products other than VenomX with zinc acetate 0.1 % by volume (*see box*).

Additionally, the four products are mislabeled because they are "offered for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written so that a layman can use the products safely for their intended uses," officials said.

MICROBIAL TESTING MISSING FOR ANTISEPTICS

The GMP problems found at Phillips' facility included not having, for each batch, appropriate laboratory determination of satisfactory conformance to final specifications for drug products. Specifically, it lacked testing for microbial attributes, including absence of objectionable microorganisms, or sterility.

"We note that your topical antiseptic drug products are indicated for use on injured skin, minor cuts, scrapes, and burns. It is essential that your drug products are tested for appropriate microbial attributes in view of their intended uses," ORA officials said.

Phillips GMP problems also include failing to:

- use equipment constructed to ensure surfaces that contact components, in-process materials or drug products are not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality or purity of the product;
- establish adequate written responsibilities and procedures applicable to its quality control unit;
- test samples of each component for conformity with all appropriate written specifications for identity, purity, strength, and quality;
- establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess;
- prepare batch production and control records with complete information relating to the production and control of each batch of drug product.

"Our findings demonstrate a lack of understanding of the basic elements of a compliant manufacturing operation, such as suitable facilities and equipment, trained personnel, appropriate components, a well-defined process, and written procedures," the warning states.

The firm did not respond to comment following requests left with Howard Phillips LLC in Arizona and with Mr. Phillips personal line. Phillips Co.'s Oklahoma facility could not be reached. Its website documents are not dated, but appear to have been updated in 2017.

The letter to Phillips, which FDA published May 16, marks a rare warning to an OTC drug manufacturer. Although FDA within the past five years conducted enforcement that led to consent decrees temporarily slowing or shutting down OTC manufacturers' operations, it submits warning letters much more frequently to firms operating other areas of its oversight – Rx drugs, dietary supplements, cosmetics, and food, tobacco and veterinary products. *(Also see "FDA GMP Warning Letters Review: Rate Soared In 2016 On Sterility And Data Integrity Concerns" - Pink Sheet, 25 Apr, 2017.)*

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NOT A TYPICAL OTC FIRM

In addition to claims rarely found for products made with OTC monograph drug ingredients, other characteristics of Phillips' operations set it apart from typical nonprescription drug manufacturers.

For instance, packaging for Phillips' four products, pictured here, lacks the color and imagery typically used on OTC drug packages.

Although it is looking for a buyer, the firm pledges on its website that "what was impossible can often become possible" in support for President Trump's Feb. 28 statement about FDA: "Our slow and burdensome approval process … keeps too many advances from reaching those in need. If we slash the restraints, not just at the FDA but across our Government, then we will be blessed with far more miracles."

And there are Phillips' claims questioned by FDA, including, with product labels linked:

- **Tetracycline-ABC** "Kills MRSA, Staph (Staphylococcus aureus), Acinetobacter baumannii, Acinetobacter lwoffi, Klebsiella pneumoniae, E. coli, Proteus vulgaris, Pseudomonas aeruginosa, Enterobacter cloacae, and Group-A strep";
- For both **Diabecline** and **TetraStem**, "With only a TOPICAL (rub-it-on-the-skin) formula, it is now possible to successfully induce stem cell therapy to treat spinal cord injury and dramatically reduce paralysis";
- "**VenomX** is an anti-venom cleanser formulated to chemically attack and dissolve the snake venom rapidly, rendering it less harmful."

FDA's OTC Naloxone Study Is A Starting Point For Other Switches, Not A Roadmap

MALCOLM SPICER malcolm.spicer@informa.com

An FDA study on expanding access to opioid overdose-reversal medication could suggest a model for Rx-to-OTC switch proposals that include some form of extra-label information, though the agency isn't going so far as saying the results will facilitate approvals for more nonprescription ingredients.

FDA Center for Drug Evaluation and Research officials said during an industry conference on May 11-12 that the agency for one year has been developing and testing labeling that instructs consumers on administering the opioid receptor antagonist naloxone through intramuscular injection or nasal delivery to a person experiencing an overdose. The study labeling includes pictograms separate from Drug Facts label (DFL) text.

"We've actually put money behind this to test this in a label comprehension study," said Division of Nonprescription Drug Products Director Teresa Michele during a panel discussion on FDA's OTC drug programs on the second day of the Consumer Healthcare Product Association's Regulatory, Science and Quality Conference in Bethesda, Md.

Pharma firms, meanwhile, often look askance at putting money behind research for novel OTC switches needed to develop some form of extra-label information, such as instructions or questions accessed online, to facilitate safe OTC use of a drug. Although FDA encourages firms to ask CDER about potential novel switch proposals for chronic conditions, such as high cholesterol, diabetes and hypertension, the agency currently does not have enough answers on criteria for success to assuage manufacturers' doubts about spending even to prepare information for a pre-new drug application meeting.

Teresa Michele, director of CDER's OTC drugs division

> "We said, 'What if we took the first step and started that development process ourselves,' so we could provide that information to companies who might be considering a switch."

Michele said the naloxone study could spur industry interest in resolving an unmet public health need by conducting tests and preparing an application for a product that would face a difficult evaluation for approval. CDER would require a potential naloxone switch sponsor to conduct its own testing as part of its application.

"We recognize that there's a barrier to switch and it's a big obstacle to some companies. We said, 'What if we took the first step and started that development process ourselves,' so we could provide that information to companies who might be considering a switch," she said.

"If there are any manufacturers who might consider this, please come talk to us," she added.

Pfizer Inc. took a swing at preparing a new drug application for a 10 mg version of its blockbuster high cholesterol drug *Lipitor* (atorvastatin) with a 1,200-subject actual use trial completed in December 2014. It halted the program and did not file an NDA after the trial did not meet its primary objectives of demonstrating patient compliance with the direction to check their low-density lipoprotein cholesterol level and, after checking, to take appropriate action based on test results. *(Also see "Light Still On For Switches After Pfizer Pulls Plug On OTC Lipitor" - Pink Sheet, 3 Aug, 2015.)*

Pfizer has not turned away from considering OTC switches for chronic conditions, though. The firm could be preparing a proposal for an OTC *Viagra* (sildenafil) indicated for erectile dysfunction, an indication **Sanofi** is targeting with its own program to develop a switch application for *Cialis* (tdalafil) on license from innovator **Eli Lilly & Co.**

PICTOGRAMS SEPARATE FROM DFL

Labels for OTC drugs, other than those intended for pediatric use with administration by an adult, typically state indications and dosing directions for the person using the product. In contrast, directions on nonprescription naloxone products would instruct a person on how to administer it to a second person. That would be similar to instructions for aphylactic shock remedies.

Those directions would include advice on signs that a person known or suspected of abusing opioid- or opiate-containing drugs could be in danger of overdosing as well as on administering the treatment.

Naloxone most commonly is administered by emergency medical personnel and by medical staff in hospitals. Several firms have approvals for intramuscular injection products. **Adapt Pharma Ltd.** has approval for a nasal delivery formulation, *Narcan* Nasal Spray, and several other firms previously had approvals only for intramuscular injection products. *(Also see "Bring Naloxone To Opioid Overdoses: FDA Crowd-Sources Smartphone Apps" - Pink Sheet, .)*

"Obviously, there are rarely health care personnel around when overdoses occur in various settings. So we need something that is broadly available that people can use quickly," said CDER Director Janet Woodcock in her conference-opening presentation.

Pictograms CDER is testing on labels show "how to safely use naloxone, including when it's appropriate to purchase it and how to use it in an emergency opioid-overdose situation," Woodcock said.

The ongoing consumer label comprehension study will provide information potentially helpful to firms interested in proposing other OTC switches. The agency will publish the study results regardless of whether the testing shows that consumers correctly self-select and use the product through the instructions and other information on the labeling.

"If it's successful then the industry can adapt it to their product," Michele said, but added that in the event the test results are not a success, "I think the labeling still will be valuable."

FDA started the work "in the face of this epidemic of deaths due to opioid overdoses" caused by either pharmaceuticals or illegal narcotics, Woodcock said. "We are very interested in getting this program complete and getting this information out there and hopefully attracting manufacturers into this space," she added.

"Pictograms CDER is testing on labels show "how to safely use naloxone, including when it's appropriate to purchase it and how to use it in an emergency opioid-overdose situation." – Janet Woodcock

NO ANSWERS YET FROM NSURE

Any ideas emerging from the naloxone study might be particularly helpful given that industry is still waiting for more guidance to come out of the Nonprescription Safe Use Regulatory Expansion initiative CDER launched in 2012.

Under NSURE, the center continues looking into potential changes in its switch application process so sponsors could propose novel switches, including ways to expand communications on safe use beyond the DFL. *(Also see "Room For Innovative Switches Could Lurk In Existing FDA Framework" - Pink Sheet, 29 Oct, 2014.)* "While there hasn't been anything out on that yet, we have been exploring internally on how to make that happen and what may be required," Michele said.

At the 2016 CHPA regulatory conference, a CDER attorney said the center was working on a framework for implementing changes, most likely requiring a rulemaking by FDA, that would allow the agency to base approval of an OTC new drug application partly on information not within a Drug Facts panel. *(Also see "CDER Talks Switches, Monograph 'More Than Ever,' But Mum On Changes" - Pink Sheet, 23 May, 2016.)*

However, neither CDER official offered an update on when FDA might propose NSURE-derived changes for the OTC switch process. "You the industry have been asking us about this for a long time," Woodcock acknowledged.

"There could be potential for restricted-access programs to aid in self-selection and other safe use areas, ways to put some guard rails in to make sure the right people are taking these medicines or directing them to a health care provider if that's what's needed," she said.

FDA realizes that without guidelines adopted in a rulemaking, pharma firms need communication directly from CDER officials on preparing a novel switch NDA.

"Because these programs do raise novel legal, regulatory and scientific considerations, we are encouraging sponsors to come in and talk on a product-by-product basis to the division while we're working out the framework for putting in those guard rails," Woodcock said.

NOVEL SWITCHES, COMPLICATED PATH

FDA was encouraging firms making Rx drugs indicated for chronic conditions to ask about potentially submitting applications to make additional ingredients available OTC before making its interest official with NSURE. *(Also see "The Future Of OTCs: Self-Selection Meets Diagnostics, Genetic Personalization" - Pink Sheet, 16 May, 2011.)*

However, agency officials have not indicated they have a solution for the conundrum drug firms eyeing OTC switch proposals must consider: when a drug is available on store shelves, health care providers aren't there to advise consumers on whether they need to use it or train them on administering it.

OTC drugs generally are indicated for symptoms easily apparent, such as a headache or cough/cold, and a product's efficacy is just as easily determined. But chronic conditions that FDA would like targeted by some OTCs are not so easily apparent and a product's treatment efficacy is a more complicated question to answer.

Novel approaches for OTC status could include the use of technology or label restrictions to help consumers correctly self-select and safely use under "conditions of safe use." Some health care groups and consumer health advocates support making pharmacists' counseling with consumers a component of novel switches, but FDA's regulatory oversight does not extend to pharmacists' responsibilities and agency officials have dismissed imposing those requirements.

Still, drug firms are aware FDA will not answer the questions Woodcock noted as inherent in novel switch applications, and thus are discouraged from investing in preparing an idea to pitch in a meeting with CDER.

Moreover, current FDA regulations prompt other investment concerns for potential sponsors of novel switch proposals: the agency could not subject eventual generic versions to the same extra-label requirements that the agency might have made for the innovator's switch, and unless a clinical trial is required for a switch NDA, the sponsor would not be eligible for any period of market exclusivity for its product. *(Also see "FDA To Tackle Critical Generics Issue In Switch Paradigm Debate" - Pink Sheet, 12 Mar, 2012.)*

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Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Considerations for evaluation of respiratory syncytial virus vaccine candidates in seronegative infants	Vaccines and Related Biological Products	May 17
Proposed protocol modifications to Sarepta's efficacy and safety study of SRP-4045 and SRP-4053 in patients with Duchenne muscular dystrophy	Pediatric, and Pediatric Ethics Subcommittee	May 18
Puma Biotechnology's neratinib maleate for single-agent, extended adjuvant treatment of adults with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy	Oncologic Drugs	May 24
Emmaus Medical's L-glutamine powder (oral solution) for the treatment of sickle cell disease	Oncologic Drugs	May 24 (afternoon)
Hospira's (Pfizer) proposed biosimilar to Amgen Inc.'s *Epogen*/*Procrit* (epoetin alfa) for all of the indications on the reference biologic's labeling	Oncologic Drugs	May 25
Novo Nordisk's *Victoza* (liraglutide) as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse CV events in adults with type 2 diabetes and high CV risk	Endocrinologic and Metabolic Drugs	June 20

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