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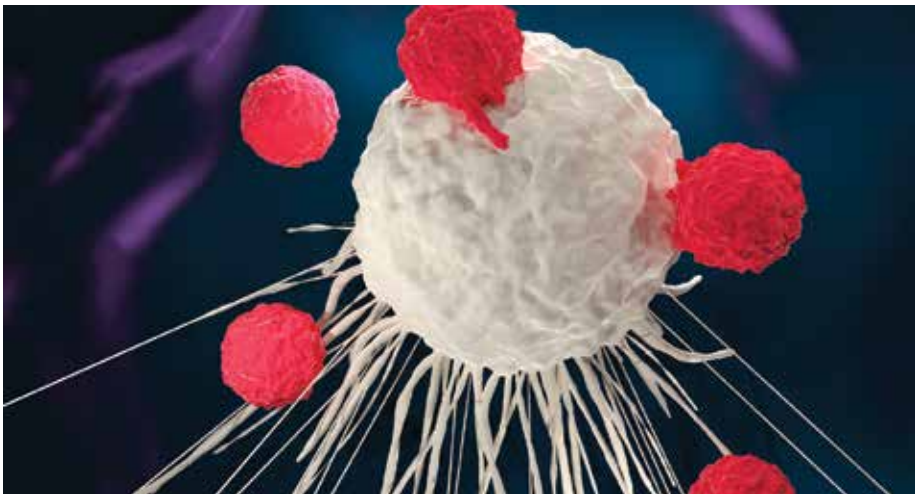

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Kite's Axi-Cel CAR-T: No Adcomm, No Problem

RAMSEY BAGHDADI pinkeditor@informa.com

July 12 was a very good day for **Novartis AG**. FDA's Oncologic Drugs Advisory Committee unanimously recommended approval (10-0) of the company's CAR-T immunotherapy CTL019 (tisagenlecleucel). *(Also see "Novartis' CAR-T Poised For The Market After Unanimous FDA Adcomm Review" - Scrip, 12 Jul, 2017.)*

The BLA for relapsed/refractory acute lymphoblastic leukemia in pediatric and young adult patients has an Oct. 3 user fee goal date but approval will probably come ahead of schedule given the oncology team's performance when it comes to cutting edge therapies.

But the outcome also served as good news for a competitor in the emerging CAR-T market: **Kite Pharma Inc.**

The company made pitch-perfect comments during an Aug. 8 second-quarter earnings call, by complimenting the outcome for another manufacturer in the same field while also underscoring the benefit to Kite and its CAR-T axicabtagene ciloleucel.

"We're extremely encouraged by the recent advisory committee meeting and its unanimous support for the risk-benefit of Novartis' anti-CD19 CAR-T therapy for pediatric ALL," Kite Executive VP-R&D and Chief Medical Officer David Chang said on the call. "We believe it was a major milestone for the field of cell therapy and provided clarity on how the agency will view this innovative therapy as it enters the commercial space."

"We have just past the midpoint of FDA review of our BLA," Chang continued. "To date, the FDA has completed its mid-cycle review, inspection of our commercial manufacturing facility in El Segundo. And the GCP inspections of our clinical sites. The FDA has informed us that they will not schedule an advisory committee meeting for axi-cel. Overall, we continue to work closely with agency as their review process moves towards the final phase."

Kite's application is for treatment of patients with relapsed or refractory aggressive non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant (ASCT).

Typically in oncology, no adcomm is a good adcomm. The trend over the last few years in FDA's Office of Hematology and Oncology Products and now the Oncology Center of Excellence has been to skip a committee stop for clear-cut homeruns. It's hard to forget how Acting OCE Director Richard Pazdur described first receiving the results for **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) when the data were truly remarkable in 2015. "I started calling up people. I called up all of the people that needed to know and I said, 'We really got to get on this. What can we do?'" he said at the time. *(Also see "FDA*

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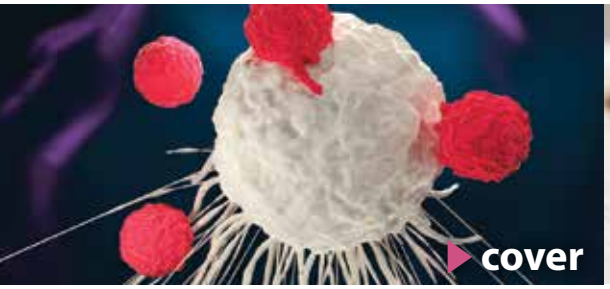
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Mylan Communications With CMS To Get Outside Review Under EpiPen Settlement

https://pink.pharmamedtechbi.com/PS121350

Corporate integrity agreement requires Mylan to have an independent body review its drug classifications and US best price determinations; settlement resolves claims Mylan misclassified EpiPen to underpay rebates. Sanofi acted as whistleblower in case.

White House Advisor Philipson Brings Industry-Aligned Views On Drug Value

https://pink.pharmamedtechbi.com/PS121328

Tomas Philipson, a University of Chicago professor and consultant to the pharmaceutical industry, is named to the White House Council of Economic Advisors.

Pharma Requests Pilot To Test Public Value Of EU Guide On Plain Language Summaries

https://pink.pharmamedtechbi.com/PS121337

The European pharmaceutical trade group EFPIA says an "initial pilot" program should be launched to test the value and impact of the draft EU guideline on presenting lay summaries of clinical trial results. The group believes that the guideline should be reviewed following the pilot, as complying with it in its current form would result in companies shelling out "significant additional resources."

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CONTINUED FROM COVER

Pazdur's Opdivo Love Affair And Other Adventures" - Scrip, 13 Nov, 2015.)

Chief Commercial Officer Shawn Tomassello made clear that Kite is ready to launch ahead of the user fee deadline of Nov. 29. "Point number one, yes, we will be launch-ready by September, to ensure that we're prepared for an approval at any time. Our commercial headquarters and field-based teams are fully staffed, trained and ready for launch." Kite expects to have a minimum of 10 centers in the US ready for the initial launch and an additional 30 sites to follow.

> ODAC is no longer viewed as a stumbling block compared to prior years. The committee has voted "yes" on all eight applications it has reviewed in 2017.

The company has clearly crossed the "Ts" and dotted the "Is" when it comes to the regulatory and reimbursement pathways that can define a commercial campaign. For example, Tomassello said the firm has held "multiple meetings" with CMS and also met with all 12 Medicare Administrative Contractors (MACs). That's the right way to do it.

"About codes and reimbursements, we feel like we have everything in place that we're going to need for people to use axi-cel and for axi-cel to be covered. And all those processes are in motion. And some things you cannot do until you actually get approval and we'll be ready to those as well."

The company even attempted to sneak in a new technology add-on payment (NTAP) in the Hospital Inpatient Prospective Payment System final rule for FY 2018, which would have required FDA approval before July.

"While Kite applied for NTAP, we withdrew our application based on the fact that we would not receive our approval before July 1, the CMS deadline. However, we will reapply for NTAP in the October time line," Tomassello said, sending another strong signal that the approval of axi-cel is imminent.

Recall that Dendreon Corp. made the mistake of *not* adequately talking with Medicare officials prior to approval of *Provenge*, which in turn triggered the national coverage decision process as senior CMS coverage officials heard about the high price through the press following FDA approval. *(Also see "Is Provenge "Reasonable And Necessary"? CMS Analysis For Medicare Coverage Seeks To Find Out" - Pink Sheet, 1 Jul, 2010.)*

Given that axi-cel looks headed toward a swift approval with coverage and payment seemingly under control, it is nevertheless somewhat perplexing that FDA took Novartis' tisagenlecleucel to panel but Kite's axi-cel gets a pass – especially since FDA has cautioned that each CAR-T product is different.

The tisagenlecleucel meeting was a milestone event for two key reasons: it was the first CAR-T application to go to panel and the first coordinated review under OCE. The meeting also made front-page news across the country as a preview of the next wave in fight against cancer. *(Also see "'Living' History: Breakthrough CAR-T Application Breaks Through In National Media" - Pink Sheet, 14 Jul, 2017.)* One would think a committee review would be more necessary for Kite since axi-cel is its first product.

An advisory committee probably would have been helpful for outside observers, the public, and oncologists in the same way as the tisagenlecleucel meeting. For example, Kite was asked if about communications regarding the advisory committee meeting with Novartis and FDA advice in relation to toxicity, toxicity management and risk management once approved.

"In their briefing documents of the Novartis adcomm, I think [the agency] tells us pretty well," Chang responded. "I would say that what we have heard from the FDA would be very consistent with what they have sort of explained during the adcomm meeting. The need for the long-term follow-up as well as having a good system to keep updating the adverse event in more or less real-time setting whilst the commercial study unfolds – commercial launch unfolds."

The benefit of the Novartis panel is it vetted those questions for tisagenlecleucel and cleared them. ODAC acknowledged the serious risks of cytokine release syndrome (CRS) and neurotoxicity but found they were manageable in light of the efficacy profile of tisagenlecleucel. Novartis also helped their cause greatly by presenting a comprehensive strategy for clinical site selection for administration post-approval and an algorithm for treating CRS rapidly. *(Also see "Novartis CAR-T Site Selection, Risk Management Are Model For Other Sponsors" - Pink Sheet, 12 Jul, 2017.)*

Kite would likely benefit from the same public vetting long-term even if approval is not in question. For example, there were cases of CRS in the ZUMA trial and one cerebral edema death previously disclosed to FDA in April. It might have been advantageous for an official panel of outside experts to sign off on the safety of the product in that instance. Such a vote of confidence would have the added advantage of protecting FDA if safety becomes an issue in the real-world setting.

Plus, ODAC is no longer viewed as a stumbling block compared to prior years. The committee has voted "yes" on all eight applications it has reviewed in 2017. That is a stunning number when you consider the committee recommended approval just five times over the past four years combined. So a panel meeting this year in oncology would not communicate the same risk to a sponsor and its supporters like it has in the past.

The most obvious reason that Kite gets to forgo a panel review is that Pazdur deems it unnecessary to inform a near-certain approval decision and scheduling a meeting will take many different re-

sources and slow the process down. Another theory is the tisagenlecleucel may not have been that helpful to FDA where the real review issues center on reproducibility and related metrics. FDA may want to use internal expertise in that regard rather than a public forum.

But FDA has also used advisory committees to profile and highlight cutting edge medicine from different sponsors or to demonstrate confidence in safety of a set of products. The agency has used that strategy in recent years with various iterations of the Hep C therapies and novel antibiotics and antivirals, as well as the first wave of biosimilars. For CAR-Ts, it appears that one advisory committee will be enough. And that's just fine with Kite.

From the editors of the RPM Report.
Published online August 11, 2017

EU Member States Taking New Steps To Tackle Drug Shortages

IAN SCHOFIELD ian.schofield@informa.com

Drug shortages are an ongoing problem in all the EU member states, and they can be caused by a range of factors, including manufacturing or distribution problems, safety concerns, and excessive exporting.

Most shortages are dealt with at the member state level by the national competent authorities, which employ a mix of different preventative or corrective approaches, such as collecting data on likely shortages, allowing the use of unauthorized medicines, and restricting exports.

The variety of tools used can make it difficult to get an overview of the situation at EU level, but a chart on shortages showing the different approaches taken by the member states, published recently by the Heads of Medicines Agencies, has thrown some light on the subject.

The information in the chart includes recent initiatives by some countries to tackle the shortages problem. Ireland, for example, says that it views the management of medicines shortages as an area of priority for public health and that this is reflected in the Health Products Regulatory Authority's Strategic Plan for 2016-2020, which includes access to health products as a key strategic goal.

In 2017, the HPRA says it intends to "take the lead in the coordination of efforts by national agencies to manage medicines shortages including the development of new initiatives and the refinement of existing measures."

Among the initiatives are improving communications in relation to shortages, engaging with stakeholders to confirm the respective roles and responsibilities, and implementing proactive measures to decrease the likelihood of shortages. "This will require improved coordination among collaborators and the HPRA are committed to the programme," and "responsibilities may change as this evolves and we will continue to provide updates accordingly," according to the information provided by the HMA.

The importance of continuity of supply is also highlighted in last year's framework pricing agreement between the Irish government and the pharmaceutical industry body IPHA, which says that suppliers who experience foreseeable or prolonged stock shortages should notify the Health Services Executive as soon as they become aware of the problem and "shall endeavour to source an alternative supply."

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The HPRA also said recently that it was offering support to companies on managing any supply problems that might arise when marketing authorizations have to be transferred from the UK to other EU markets as a result of Brexit. *(Also see "Irish Regulator Prepares For Brexit-Related Problems, Offers To Take On More EU Work" - Pink Sheet, 3 Aug, 2017.)*

NEW SHORTAGES CENTER IN THE NETHERLANDS

In the Netherlands, in January this year the regulatory agency (MEB) and the Health Care Inspectorate launched a new Medicine Shortages and Defects Notification Centre. "All notifications submitted to this notification centre are coordinated by both authorities in order to inform the public in case the unavailability might cause problems for the treatment of patients or subgroups of patients," the HMA table notes.

Where cases of non-availability are notified to the new body, the MEB says it will look for possible alternative products in the same therapeutic category (for example a different strength or formulation).

Romania's National Agency for Medicines and Medical Devices (NAMMD) set up a database in June 2016 for notifications of medicine shortages, which is accessible via the agency's website. The database was established on the basis of information provided by marketing authorization holders (MAHs) under Romanian Law 95/2006 on healthcare reform. All medicine shortages involving Romania are managed by the Ministry of Health through the agency, which receives all relevant notifications from MAHs. The NAMMD has also begun an operational initiative on behalf of the ministry, consisting of an e-mail address (medicineshortages@anm.ro) where patients and healthcare professionals can contact the agency about shortages in their area.

In September 2016, the ministry also launched a website with the same objective of monitoring drug shortages on the Romanian market. The NAMMD has a procedure in place to monitor shortages of medicines for which there is no alternative for the same INN on the market. In such cases, the NAMMD informs the ministry, which estimates the amount of the drug required for a specific period of time, up to a maximum of one year. Based on this estimation, the NAMMD issues an authorization for special needs.

In January 2017, an amendment to the Slovakian medicinal product law came into force, stating that only medicinal products for human use that are on the reimbursement list can be exported. Export of the product must be carried out by the manufacturer of the drug, the MAH or by the wholesaler, if such export has been authorized. The national regulatory agency, SUKL, does not allow the parallel export of medicinal products if they are in short supply and re-export could "threaten the availability and safeguarding of public health."

Belgium has had a national task force in place since 2013 which involves all stakeholders as well as the reimbursement authorities. Where availability might cause concerns in terms of public health, the regulatory agency, FAMHP, monitors the situation in conjunction with the MAH.

The most common solution to medicines shortages in Belgium is to import from another member state, but other solutions are being considered, such as the establishment of a list of essential medicines for which exports would only be allowed if it was shown that sufficient quantities had been supplied at national level to meet patient needs. A "risk management plan with regard to manufacturing problems or delays due to quality and/or safety reasons might also constitute a best practice for MAH/manufacturers."

In March this year, the Czech president signed off an amendment to the Medicines Act that gave the health ministry the ability to ban the parallel export of specific medicines where there is a risk of shortages on the domestic market. *(Also see "Czech President Signs Law Limiting Medicine Re-Exports – But Will It Work?" - Pink Sheet, 20 Mar, 2017.)*

From the editors of Scrip Regulatory Affairs. Published online August 16, 2017

Medically Senseless: Why EU Pediatric Investigation Plans Should be Abandoned

KLAUS ROSE pinkeditor@informa.com

This year the European Commission is due to report on how the EU Paediatric Regulation is faring 10 years after it came into force.

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Since 2007, the European Medicines Agency recommends the marketing authorization of new drugs only if they are accompanied by a pediatric investigation plan (PIP) approved by its pediatric committee (PDCO).

Drug regulators in the EU claim PIPs are needed because of "neglect of children in the development of effective and safe medicinal products" or "lack of availability of appropriate medicines for children." Such statements are medically wrong. Pediatric medical treatment is continuously improving. How could statements in open contradiction to reality exert so much influence?

This year the European Commission is due to publish a report on how the EU Paediatric Regulation (Regulation (EC) No 1901/2006) is faring 10 years after it came into force in 2007. This provides an opportune moment to discuss why the PIP system needs a thorough revision.

THE "THERAPEUTIC ORPHANS" DOGMA

The idea of running separate clinical trials in adults and children can be dated back to the aftermath of the thalidomide catastrophe that led to the 1962 US legislation that mandated clinical testing of new drugs before registration. This law also transferred control of drug advertising to the US Food and Drug Administration.

From 1963 on, US pediatrician Harry Shirkey pointed out that

warnings against pediatric use were placed on drug labels, concluded that these denied the use of new drugs to children, and called children "therapeutic orphans."

Shirkey's view was taken up by the American Academy of Pediatrics, which claimed that the bodies of minors – from newborns to adolescents – are so different from those of adults that they need separate proof of safety and efficacy (S&E). The AAP stated in its 1995 guidelines on ethical conduct in pediatric studies: "There is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents."

But Shirkey also observed that most physicians ignored the pediatric warnings. Indeed, legally these warnings did not prohibit use in children. They prevented the advertising of medicines for pediatric use (which the FDA has controlled since 1962), and prevented damages lawsuits in the litigation-prone US.

The AAP and the FDA collaborated closely in the belief that minors needed pediatric labels based on separate S&E studies. Later, the FDA defined pediatric age as under 16 years in the Federal Code of Regulation (201.57(f)(9) CFR); in the US legal adulthood is regulated at the state rather than the federal level.

Eventually, the US pediatric legislation promised financial rewards (pediatric exclusivity, a patent extension) for pediatric regulatory studies. But the therapeutic orphan concept equated the contemporary legal term "children" with a medical/physiological term. Newborns' bodies are indeed different from those of adults; less so in the case of school-age children and even less so for adolescents.

The therapeutic orphans were/are a misleading blur at the interface of law and medicine: demands for separate S&E studies in all minor age groups were/are based on exaggerated AAP statements. In 1995, for example, the AAP "proved" in its 1995 guidelines on pediatric studies that any drug used in minors without sufficient pharmacology studies posed the risk of toxicity and death by referring to just two publications on antibiotics in preterm newborns: this was a bold extrapolation from babies to anybody under the age of 16.

The human body matures and becomes adult before the person's 16th birthday. Why should antibiotics, cytotoxics, or creams work in adults and not in adolescents or school children? The therapeutic orphan blur reflected clinicians' uncertainty about the methodology of clinical trials: pediatric clinical pharmacology (PCP) had just started. Minors need data on dosing and safety, not separate proof of S&E. Since 2006, the FDA allows extrapolation of efficacy of anti-epileptics from adults down to four years of age and has licensed an anticancer compound down to 12 years based on adult plus additional population pharmacokinetic (PK) data. The FDA has not revised the general therapeutic orphans concept.

Pediatric use of drugs that received US pediatric exclusivity was and remains very limited. Children and adults have predominantly different diseases.

"PIPs demand separate efficacy, safety and other studies in minors as if they were another species. Some lack medical sense simply upon analysis of the inclusion criteria."

THE PROBLEM WITH PIPS

The EU Paediatric Regulation took up, intensified and expanded the therapeutic orphans/US pediatric legislation approach. It defines the "pediatric population" as everybody between birth and 18 years. PIPs demand separate efficacy, safety and other studies in minors as if they were another species. Some PIP-demanded studies lack medical sense simply upon analysis of the inclusion criteria.

For example, a number of PIPs require studies in patients with a physiologically mature body, but who are still under 18. These are not "pediatric" patients, nor are these "pediatric" studies. They reflect a "territorial" attitude, as if these patients "belong" to the PDCO. Recruitment to these studies is based on legal, not medical criteria.

In the case of dermatology, for example, one PIP (EMEA-000585-PIP01-09) demands an active controlled study on efficacy, tolerability and quality of life in 12-17 year olds for a cream against solar urticaria.

Another (EMEA-000892-PIP01-10) requires two S&E studies in 12-17 year olds with acne, while EMEA-001624-PIP01-14 demands five S&E studies for a monoclonal antibody (MAB) in 2-17 year olds with atopic dermatitis, and EMEA-000415-PIP01-08-M01 requires one S&E study with immunoglobulin in 2-17 year olds with myositis.

These efficacy/S&E studies are medically senseless. Creams, MAbs and immunoglobulin work the same before and after the 18th birthday. Dosing in <12 year olds can be assessed by PK and pharmacodynamic (PD) modeling. Most essential safety issues are already known from the adult pivotal trials. Additional safety issues in children of school age will not be detected in separate regulatory studies. For this, registries are a much more appropriate method.

EMEA-000366-PIP04-12 demands one PK-PD modeling study and one population PK modeling study for adalimumab in 12-17

ABOUT THE AUTHOR

Klaus Rose is a medical doctor with postgraduate degrees in general medicine and pharmaceutical medicine. He was global head of pediatrics at Novartis from 2001 to 2005 and at Roche from 2005 to 2009. He is now an independent pharmaceutical consultant.

year olds. Compared with the five S&E MAb studies, they may appear modest. But are they medically necessary?

The alleged need for separate S&E studies in minors is based on flawed, scientifically indefensible AAP claims, worsened by the EU legislation's extension of the "pediatric" age range. Most PIP-demanded studies are "only" medically senseless (and therefore unethical). Even worse are studies in diseases that are so rare in minors that there are not enough patients for multiple PIP studies.

For example, 12 melanoma PIPs have been published. Two melanoma studies were terminated in 2016, while four continue recruiting minors with melanoma and other solid tumors. PIPs demand unfeasible studies in pediatric psoriasis, leukemia, multiple sclerosis and any disease frequent enough in adults to attract drug development, but rare in minors. To identify such studies, all PIPs for the same disease need to be examined. The examples above are the tip of the PIP iceberg: more research will corroborate these findings.

For allergens for specific immunotherapy, PIPs demand five-year placebo-controlled studies in tens of thousands of children and adolescents, exposing patients on placebo to the risk of progression to asthma. The EMA's 10-year report on experience with the Paediatric Regulation claims that 238 new medicines for use in children have been authorized in the EU. But there are no 238 new medicines for children: they simply obtained pediatric labels. To what degree this improves clinical care is not even addressed. Page 14 of the report lists the "achievements" so far, saying that "many medicines have become available after PIP completion for the treatment of infectious diseases." But the products themselves existed before, i.e., they were "available". A new asparaginase product has allegedly become "available" for acute lymphoblastic leukemia (ALL). But ALL has been treated with asparaginase for decades, achieving survival rates of 90% before the PIPs started. The EMA 10-year report is misleading, at best.

CONFLICTS OF INTEREST

The flawed AAP statements reflected concern for children's health and a wish for pediatric research, research funds, and an AAP-controlled monopoly on clinical investigations: a clear conflict of interest.

Budgets for institutions, including regulatory authorities, are assigned on the basis of their perceived value to the public. In the US, with its checks and balances, the US pediatric legislation had initial positive outcomes.

> "Companies are tempted to accept questionable PIPs as annoying but affordable additional costs of drug development."

The EMA is a supranational, more insulated entity. The EMA uses the AAP's moral imperative in PIP negotiations as if the EMA represents the high moral ground and the pharmaceutical industry the opposite. An alleged lack of appropriate medicines for children is claimed by employees of the EU regulatory authorities connected to the PIP system. The EMA claims that off-label use of medicines in children is dangerous in general, in open contradiction to clinical reality: most pediatric sub-specialties developed with off-label drug use.

The AAP has a clear, pragmatic position towards off-label use. The European Academy of Pediatrics by contrast does not have a position on either off-label use or PIPs. The desire of the EMA and the EU national regulatory authorities to emphasize their role in public health, as well as clinicians' conflicts of interest, have so far been ignored in the PIP discussion.

Initial scepticism, partially based on traditional/archaic protective instincts, has given way to an enthusiastic welcome for pediatric research. But minors need reasonable studies, not as many studies as possible. The concept of drug treatment for rare, pediatric, and rare pediatric diseases has been deep-frozen since 1963 by the therapeutic orphan blur at the interface of medicine and law.

Specialists successfully used whatever medicines were available, while pediatric clinical pharmacology expanded partially through the US and EU pediatric legislation. Academia always needs money; industry funding was welcome, without considering potential conflicts of interest: for the individual academic clinician, participation in a clinical trial brings opportunities of publishing, networking, and funding. But if the trial harms patients, as is the case with unfeasible studies or studies that prevent effective treatment, this is done on the back of the patients, which is unacceptable.

Companies are tempted to accept questionable PIPs as annoying but affordable additional costs of drug development. So far, this has worked. But what about patients recruited into questionable studies? When US parents learn about the medical senselessness of such trials, they will sue. If a company cannot prove that it pushed back, US judges might hand out punitive damages, which can ruin a company, a hospital, an institutional review board (IRB) or an ethics committee (EC).

THE NEED FOR COMPANIES TO TAKE A STAND

Companies should take steps to defend patients against unfeasible/unethical PIP study requests, for both ethical and long-term economic reasons. Large companies have learned to live operationally with PIPs, but at the cost of patients' health. Backlashes by parents' lawsuits are inevitable, specifically so in the US where patients' rights and the legal system allow strong damages lawsuits, including punitive damages.

Companies need more self-confidence. The EU pediatric legislation allows the EMA to enforce medically senseless studies. Companies cannot register without a PIP; during PIP negotiations they must

> "Backlashes by parents' lawsuits are inevitable, specifically so in the US where patients' rights and the legal system allow strong damages lawsuits, including punitive damages."

"propose" studies. But the law doesn't coerce them to play theater, to pretend to share the EMA/PDCO's pseudo-scientific position.

Companies should express their thoughts openly. During PIP negotiations, they should "propose" studies but they should share their concerns before the study starts with the respective IRB/ECs, who mostly are not yet aware of the general danger PIPs represent for underage patients. IRBs/ECs will learn. They can and should reject unfeasible PIP studies, and suspend ongoing ones.

EMA/PDCO insist in negotiations that their position is based on science, which is often not the case. So far, some single IRBs/ECs have rejected PIP studies. Once rejections become more frequent, negotiations and modifications will become easier. EMA management is aware that prolonged confrontations with IRBs/ECs would be detrimental to its reputation.

So far, bodies representing the pharmaceutical industry have tried to alleviate the operational PIP burden, but there are limitations to what they can do. The EMA is expanding the PIP obligations by further revoking class waivers: from 2018, PIPs will be required for diseases that are extremely rare in minors, such as liver cancer. Industry bodies need to look again at the PIP system and the therapeutic orphans concept and should lobby for a fundamental revision.

Similarly, EU national professional bodies representing pediatricians and physicians should distance themselves from the PIP system and ask for it to be revised. Pediatricians who aspire to a leadership position in future need to learn about these areas. Within pediatric academia a debate needs to be started about questionable PIP studies and conflicts of interest when clinicians participate in them.

NON-EU REGULATORY AUTHORITIES

Better scientific understanding of the challenges of pediatric drug development outside of the AAP, therapeutic orphans and PIP schemes is needed. The intellectual flaws in the AAP's guidelines need to be addressed. The FDA should stop collaborating in the "pediatric cluster" with the EMA, which also involves regulatory authorities from Japan, Australia and Canada. Also, the US pediatric legislation needs a critical re-assessment.

Non-payment of minors' treatment by reimbursement institutions or menacing lawsuits because drugs are not licensed in children were two out of five arguments put forward during a conference on pediatric clinical pharmacology in 1997 as a justification why pediatric labels are necessary. These are legal, not medical challenges. They can and need to be addressed by legally allowing physicians to use their experience to assess the maturity of the patient's body, independent of the patient's date of birth. Regulatory authorities worldwide should reject unethical PIP studies and suspend ongoing ones.

The longer the PIPs system continues, the more the EMA's public image will be damaged. It would be desirable for the EMA to propose the immediate abandonment of the PIP system, but the chances that this will happen are remote.

CONCLUSION

We need to re-consider the role of labels in pediatric healthcare, specifically in rare diseases where large safety and efficacy trials are unfeasible, and in patients who get diseases before legal adulthood. Who in 1962 would have imagined that one day there would be effective drugs against lethal diseases such as melanoma or chronic myeloid leukemia? There are too few minors with these diseases for systematic S&E studies.

To nevertheless treat minors with such drugs does not make them therapeutic orphans. The therapeutic orphans concept, the insistence on separate S&E studies in children, and the automatic requirement for PIPs are becoming an obstacle to progress in healthcare.

Revision of the therapeutic orphans concept is a societal task. Revising the EU pediatric legislation will require a change in scientific assessment and in public opinion. Pediatricians, pharmacists, industry and authorities will need to conduct an intense dialogue on such changes, but not under the pretense that tighter regulation is necessarily good for children.

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

Par Alleges 'Shocking' Trade Secret Theft By QuVa Pharma

BRENDA SANDBURG brenda.sandburg@informa.com

Par Pharmaceutical Inc. began to investigate potential trade secret theft by QuVa Pharma Inc. after FDA granted QuVa's request to allow vasopressin to be used in compounding and numerous employees involved in development of Par's *Vasostrict* (vasopressin injection) jumped to QuVa.

Par, a subsidiary of **Endo International PLC**, alleges in an Aug. 14 suit against QuVa and three of its employees that they could not have developed a vasopressin drug product without using Par's trade secrets. Par seeks an injunction restraining the defendants from using or selling its trade secrets or other proprietary information; an order requiring the defendants and their employees to return Par's trade secrets and other confidential materials; an injunction preventing them from destroying or altering any evidence; and an award of damages, including punitive and exemplary damages.

The complaint says that while Par's investigation is ongoing, "the results to date have been shocking and have led Par to conclude that defendants are engaged in actual and threatened misappropriation of the trade secrets and other confidential information."

QuVa, a compounding company, was formed by former Par employees Stuart Hinchen and Peter Jenkins, who had been the CEO and chief development officer, respectively, of JHP Group Holdings Inc, which Par acquired in February 2014 and renamed Par Sterile. JHP submitted a new drug application for Vasostrict to FDA in September 2012 and it was approved in April 2014.

Jenkins resigned from Par Sterile on June 6, 2014 and Hinchen resigned a few days later. Par said that about or before the time of their resignations, "Hinchen and Jenkins began secretly planning and preparing to launch a new pharmaceutical company that would compete with Par for business from hospitals and other healthcare providers using a hybrid 'compound manufacturing' model to avoid the time and expense of going through the rigorous FDA new drug approval that applies to drug manufacturers such as Par Sterile."

Before resigning from Par, the complaint says, one employee forwarded three internal Par PowerPoint presentations with trade secrets, including supply chain metrics, monthly finances and budgets, and plans relating to planned new product launches.

The complaint says Hinchen and Jenkins incorporated QuVa in July 2015 and shortly thereafter announced the acquisition of a sterile drug compounding facility and a manufacturing facility. It says QuVa has poached at least nine Par Sterile executives, managers, and consultants with intimate knowledge of the trade secrets and other confidential information regarding sterile manufacturing, Vasostrict, and Par's other vasopressin products.

'I'LL STEAL WITH PRIDE'

One of QuVa's recent hires is former Par Sterile Senior VP and General Manager Mike Rutkowski, who left Par on April 14 and is also named as a defendant in the complaint. The suit says that internal Par email records show that in the months leading up to his departure, Rutkowski disclosed highly confidential and proprietary information relating to manufacturing and storage methods, operating details and results, and business strategies for Vasostrict. It says he also downloaded numerous Par documents to a personal hard drive within days of giving notice that he was leaving the company.

The complaint cites a March 9, 2017 email exchange between Rutkowski and Donna Kohut, a former Par Sterile consultant who had joined QuVa. The suit alleges that Rutkowski provided Kohut with Par trade secrets and confidential information on how to pass an FDA facility inspection. That email was in response to an earlier email in which Kohut included an internal QuVa announcement that a QuVa facility was "in operation." The suit says "Rutkowski responded 'Way to go team!!!!!!!!!!!!!!,' evidencing that by at least March 2017 Rutkowski considered his 'team' to be QuVa, not his employer Par Sterile."

In a March 15 email, the complaint says Rutkowski forwarded to Kohut three internal Par PowerPoint presentations with trade secrets, including supply chain metrics, monthly finances and budgets, training and personnel developments, and future business plans relating to planned new product launches, including vasopressin products.

"In reply, QuVa's Kohut candidly announced, 'I'll steal with pride just like you taught me," the complaint says, to which Rutkowski replied, "'LOL Love it!!!!!'"

The suit states that on April 19, five days after Rutkowski's departure, QuVa submitted a letter to FDA seeking to add vasopressin to a list of active ingredients for drug compounding. The complaint says that although the letter was "rife with factual misrepresentations," FDA relied on it in deciding to add vasopressin to its bulk drug substances list dated as of July 1, 2017, indicating that it is now un-

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der "Category 1" of bulk drug substances under evaluation, which means FDA does not intend to take action against an outsourcing facility that compounds it while it is under evaluation.

TRADE SECRETS NECESSARY FOR COMPOUNDING, PAR SAYS

Vasopressin was marketed as a therapeutic prior to enactment of the Food, Drug, and Cosmetic Act of 1938. In 2011, FDA issued guidance that it would begin to encourage manufacturers of such products to obtain the required evidence and comply with the approval provisions of the FDCA or remove the products from the market.

Vasostrict, the first and currently only vasopressin injection approved by FDA, is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who reman hypotensive despite the administration of fluids and catecholamines.

Par says it is impossible for Hinchen, Jenkins and Rutkowski and the former Par Sterile employees they hired to perform their duties at QuVa in compounding a vasopressin product without using or relying on Par's trade secrets.

Based in Sugar Land, Texas, QuVa describes itself as "the leading industry 503B platform and partner of choice for compliance-oriented healthcare facilities looking to ensure a quality, safe and consistent supply of medications."

Under Section 503B of the 2013 Drug Quality and Security Act, a compounder can become an outsourcing facility. Drugs compounded by an outsourcing facility can qualify for exemptions from FDA approval requirements and the requirement to label products with adequate directions for use, but not from current good manufacturing practice requirements.

QuVa did not immediately respond to a request for comment on the suit.

Par's suit is the latest in a recent string of pharma trade secret theft suits. In February, **Pfizer Inc.** filed suit against its former global marketing director alleging she emailed documents to herself and copied hundreds of files on product launch plans and steps to obtain government approvals. *(Also see "Ex-Pfizer Employee Overseeing Xeljanz Global Marketing Sued For Trade Secret Theft" - Pink Sheet, 1 Mar, 2017.)* She subsequently agreed not to disclose Pfizer's trade secrets and the suit was dismissed. *(Also see "Pfizer Ex-Marketing Director Agrees To Injunction, Ending Trade Secret Suit" - Pink Sheet, 29 Mar, 2017.)*

And in March, **Amgen Inc.** sued **Coherus BioSciences Inc.** and its manufacturing partner **KBI Biopharma Inc.** claiming they hired approximately 100 former Amgen employees, at least eight of whom allegedly stole Amgen trade secrets via USB drives. *(Also see "Amgen Alleges 'Massive Conspiracy' By Employees Who Joined Coherus And KBI" - Pink Sheet, 8 Mar, 2017.)* That case is ongoing.

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South Africa To Tighten Up On Patenting To Promote Innovation, Improve Medicines Access

IAN SCHOFIELD ian.schofield@informa.com

The South African government has unveiled the first phase of its draft intellectual property policy which is intended to ensure that the country defends IP rights and promotes innovation while also protecting public health and improving access to medicines.

Among the key proposals are closer scrutiny of patent applications, tighter criteria for patentability, more use of voluntary and compulsory licensing, tougher disclosure requirements, and measures to build up local drug manufacturing capacity.

The draft policy, which will be put out for a 60-day consultation period once it is published in the Government Gazette, also looks at how competition and patent law can be used together to implement the flexibilities in the TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement, and seeks to ensure that South Africa's regional and bilateral agreements do not incorporate any IP standards that go beyond TRIPS.

> "Some key aspects, if improperly implemented, could negatively impact producers of innovative medicines and are thus cause for concern" – IFPMA

The government freely admits that it has not done enough to implement a fully-fledged IP framework, noting that the intersection of IP and public health "has long been an issue of contention within South Africa, and one without resolution to date."

The Department of Trade and Industry says that although there are already many IP protections in place in South Africa, "there is a need for a comprehensive IP policy that will promote a holistic, balanced and coordinated approach to IP."

The publication of the draft policy has been welcomed by industry and health activists alike, albeit with some reservations. Konji Sebati, CEO of the South African R&D-based industry body IPASA, said she believed that "in the end it will be a balanced policy that will ensure innovators are rewarded for their biopharmaceutical discoveries while on the other hand ensur-

ing that these innovations are available to those who need the treatments."

However, she told the *Pink Sheet* that IPASA had raised several concerns in some areas and that others still needed clarity, "because we believe the process is not a punitive process as we have been assured, but indeed a process that will ensure balance." Areas where the association still wanted to engage with the drafters of the policy included patentability criteria ("a continuing source of misconceptions"), parallel importation, exceptions, voluntary and compulsory licenses, patent opposition, and IP and competition law, "to name a few."

The international pharmaceutical industry federation, IFPMA, had similar reservations. While it supported many of the policy's objectives – such as creating an environment conducive to economic opportunities, attracting investment, promoting R&D and innovation, and increasing public awareness of IP in South Africa – it said that some key aspects, "if improperly implemented, could negatively impact producers of innovative medicines and are thus cause for concern."

Ellen 't Hoen, a health advocate who was the first director of the Medicines Patent Pool, said that South Africa had been "a champion internationally for public health friendly approaches to the protection of intellectual property," but that so far this had not been reflected in domestic practices. "The IP policy is clearly set out to change this and fix domestic patent law, 't Hoen commented. "It addresses a wide range of issues that has the potential to affect positively the availability of and access to lower priced medicines."

THE DRAFT POLICY

The overall IP policy is intended to build on key government reforms like the National Development Plan (NDP), the New Growth Path Framework (NGP), and the National Drug Plan. It will be implemented in phases, with this first phase covering IP and public health, coordination in international fora, and the implementation of commitments undertaken in international agreements.

Intellectual Property is "an important policy instrument in promoting innovation, technology transfer, research and development (R&D), creative expression, consumer protection, industrial development and more broadly, economic growth," the DTI says.

> "SSE will ensure that the public interest is served by ensuring that the patent system truly promotes innovation" – draft national IP policy

It notes that paragraph 4 of the Doha Declaration on TRIPS and Public Health states that the TRIPS agreement does not prevent members from taking measures to protect public health and that it should be interpreted and implemented "in a manner supportive of WTO [World Trade Organization] members' right to protect public health and, in particular, to promote access to medicines for all."

Nonetheless, the DTI says, the South African government has not made full use of the flexibilities available in trade rules by pursuing appropriate national policy and legislation, "despite a constitutional imperative to increase access to medicines as a component of the state's obligation to take reasonable measures toward the realization of the right to healthcare services."

The policy therefore aims to ensure that South Africa protects IP rights "and at the same time achieves its objectives of promoting national development imperatives, which include, among others, boosting local manufacturing, promoting innovation and ensuring equitable access to medicines. This will require the development of an appropriate framework for granting patents."

PATENT SEARCH AND EXAMINATION

One of the key proposals in the patents area is to tighten up on the examination of patent applications. The government admits that it is "a matter of much debate that South Africa does not conduct substantive search and examination (SSE) prior to the grant of patents."

The introduction of SSE will result in greater legal certainty for patent owners and "ensure that the public interest is served by ensuring that the patent system truly promotes innovation," the document says. "It is crucial to work toward the adoption of SSE. The underlying policy rationale of patents is to serve as an incentive to stimulate innovation, and SSE is a key tool to ensure this objective is met."

Rejecting concerns expressed by some stakeholders that only patent applications in only one field of technology – pharmaceuticals – would be subject to full substantive examination, the DTI says that in fact the intention is to "identify a range of strategic sectors for full SSE, including and beyond the health sphere, based on capacity within government, as well as development and public interest considerations." As the government's capacity expands, the fields subject to full substantive patent examination will be expanded.

PATENT OPPOSITION

Another key reform in the patent area is the introduction of pre- and post-grant opposition procedures, which the government says can help to gather all information and expertise relevant to the application for or grant of a patent, provide "some degree of certainty regarding the validity of a patent," and save time on "expensive patent revocation proceedings."

Most importantly, it adds, "such proceedings seek to ensure that only those inventions that meet domestic statutory requirements for patentability are granted patent protection."

The policy recommends that eventually opposition proceedings will be enacted in the law both before and after the grant of a patent. In the meantime, because of "capacity constraints," it recommends that patent law recognizes a third-party submission system or "observation" to stand in for the pre-grant opposition process and for existing provisions in administrative law to be used in lieu of post-grant oppositions.

TIGHTER PATENTABILITY CRITERIA

Also proposed are stronger patentability criteria to be implemented in the process of examining patent applications. These are intended to promote "genuine" innovation, "strike the optimal level of IP protection," and "balance the rights of IP holders and users alike." The new criteria would form part of the Patents Act.

At present, South Africa has a "depository system" where the subject of a patent application is only examined against the substantive criteria of novelty, inventive step, and industrial applicability if the patent is challenged in litigation.

This, the government says, has "substantial drawbacks" for both producers and users of IP. For producers, the lack of examination "calls into question the integrity of their patents, since the grant of a patent does not guarantee that the subject of the patent meets patentability criteria in the country, or that it does not contain subject matter excluded by law," according to the draft policy.

"Indeed, a leading South African university recently conducted a study which found that a significant number of patents granted in South Africa would not pass muster under an examining system," it says.

"Users of IP are prejudiced on the other hand because subject matter that should be in the public domain can be unfairly monopolised by exclusive rights. Moreover, the underlying policy rationale of patents is to serve as an incentive to stimulate innovation."

The document notes that various countries periodically review and adapt the application of patentability criteria to achieve appropriate levels of patent quality. "One interesting example is Australia, which, in 2012 adopted legislation which upwardly adjusted standards for patentability," the policy says. A recent report by Australia's Productivity Commission showed that the 2012 reforms did not adequately "raise the bar" and "hence the same jurisdiction is currently considering further changes to the inventiveness test in its patent law."

The draft policy also suggests tighter disclosure requirements whereby applicants would be asked to provide information on the status of similar and related patent applications in other international jurisdictions.

"Article 29(2) of TRIPS provides that members may require a patent applicant to provide information concerning the applicant's corresponding foreign applications and grants. South Africa's patent legislation does not oblige applicants to furnish such information," the DTI says. "As we move toward SSE, requiring the provision of pertinent information about corresponding patent applications and grants is recommended."

STAKEHOLDER REACTIONS

IPASA's Sebati said the association supported the proposals for substantive search and examination "because we too do not want to see a country flooded with spurious, falsified and counterfeit medicines. We believe this will also turn the arguments and/or attempts to rubbish incremental innovation on their heads since these incremental innovations will also have to pass the rigorous patentability steps." She added: "South Africa is also party to several multilateral treaties on IP, and we believe it will not wish to be singled out as non-compliant."

The IFPMA similarly said it supported an SSE system in South Africa, but cautioned that there needed to be "appropriate expertise and infrastructure in place." Timelines for patent examination had to be properly regulated and predictable and the government had to ensure that "technological sectors will not be unfairly treated."

On patentability, the federation said the new criteria should be the same as those required for other fields of technology – i.e., novelty, inventive step, sufficiency of disclosure and industrial utility. Requirements going beyond these criteria would "run contrary to South Africa's international obligations and could have a very negative impact on pharmaceutical innovation."

The Fix the Patent Laws Campaign, a group of activist bodies including Médecins sans Frontières, the Treatment Action Campaign and the Cancer Association of South Africa, lauded the planned implementation of a system of SSE in order to ensure compliance with existing law and "to ensure that only applications deserving of patent protection are granted."

It agreed with the proposed incremental approach, "which we submit can be achieved by starting with the pharmaceutical sector and by considering outsourcing of the examination of applications for patents."

FPLC also gave its support to the proposal for pre- and post-grant opposition procedures, saying that third parties, "which could include generic companies and civil society groups," would be able to "assist the patent examiner in the decision-making process." The group called for a cost-effective procedure and "wide access to information concerning patent applications to enable third parties to intervene."

As for the proposal to develop patentability criteria, FPLC said that this would "lead to fewer poor quality or ever-greening patents being granted in South Africa" and "only true innovations will be rewarded with patent protection."

't Hoen told the *Pink Sheet* that the most important changes in the policy were those related to plans to "introduce substantive examinations of patent applications and move away from the depository system South Africa has had to date."

This, combined with plans to implement strict patentability criteria conducive to public health and provide for pre- and post grant oppositions to patent applications, would "help to improve the quality of pharmaceutical patents, which is good for the IP system and good for public health," she declared.

> "Patentability criteria will lead to fewer poor quality or ever-greening patents being granted in South Africa" – FPLC

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Switching, Substitution & Quotas: Irish Govt Wants Views On Boosting Biosimilars

IAN SCHOFIELD ian.schofield@informa.com

The Irish government has finally begun a consultation on the development of the country's first national biosimilars policy, with stakeholders being asked for their views on possible ways of stimulating the biosimilars market, such as switching, substitution, prescribing quotas and tenders.

Health minister Simon Harris said that an "evidence-based National Biosimilar Medicines Policy" would provide "clarity and certainty to the health service, industry and patients on the use of biosimilars and will ensure that government remains focused on its commitment to deliver greater value for our pharmaceutical spend."

The recently formed association representing generic and biosimilar firms, Medicines for Ireland, welcomed the consultation but said it was long overdue. "Biosimilars have been on the market in the EU since 2006," said its co-chair, Sandra Gannon of Teva Ireland. "It has taken over 10 years to get to this consultation stage."

It's not clear why the government has taken so long to get to this point, particularly as it is well aware – as shown by the examples cited in the consultation paper – of the wide range of tools that are available to boost biosimilar usage and that other EU countries have been using for some time.

Harris said in September last year that the department of health was developing a biosimilars policy and looking to "create the right market conditions that will enable the biosimilar industry to grow, just as the rest of the pharmaceutical industry has been supported to grow." *(Also see "Ireland Prepares New Biosimilar Policy To Improve Access, Boost Industry" - Pink Sheet, 29 Sep, 2016.)*

More recently the minister said that biosimilars were "key to the future of high-tech medicine spending" and that the new policy should be rolled out by the end of this year. *(Also see "Irish Health Minister Speaks About EMA Relocation, Drug Pricing, and Boosting Biosimilars" - Pink Sheet,, 13 Jul, 2017.)*

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> "It is "essential that these resources invested in medicines are used efficiently and effectively" – Irish government

Announcing the consultation, the government noted that the community medicines bill is forecast at just over €1.7bn this year, and said it was "essential that these resources invested in medicines are used efficiently and effectively."

While the overall bill has remained relatively stable since 2012, spending on high-tech medicines has increased, rising from €442m in 2013 to €597m in 2016, and this will "raise significant challenges in future years, driven primarily by the increasing volume of existing medicines in addition to the high cost of the future pipeline of new medicines," says the consultation paper, which is out for comment until Sept. 22.

Many of the most frequently prescribed medicines have lost, or are due to lose, patent protection, and more than €200m is currently spent on biological drugs that have a biosimilar available or due to come available in 2018.

"Despite the opportunities presented by biosimilars, uptake in Ireland remains low in comparison to many [EU] member states," the government says, adding that while the EU has approved 28 biosimilars, only 11 are currently reimbursed in Ireland.

The paper outlines a range of possible options for increasing the use of biosimilars, citing the various tools already in use in a number of other member states. It asks stakeholders for their views on a range of issues, noting that an "appropriate mix of policy levers for Ireland will be required" to address the situation, and that "respondents are asked to consider the individual

policy lever, the form it should take and how it would interact with other levers."

SWITCHING AND SUBSTITUTION

Tackling two of the most obvious mechanisms for increasing biosimilar uptake, it notes that the Irish Health Products Regulatory Agency supports physician-led switching of biologicals and biosimilars provided the change is made in consultation with the patient, but that it does not recommend patients are switched back and forth between a biosimilar and a reference medicine.

As for practices in other EU countries, it notes that "Poland encourages switching existing patients to biosimilars at every therapeutic level," while in Belgium and Spain switching "is not generally recommended" but the decision is up to the doctor.

Regarding the more thorny issue of pharmacy substitution, it says that the Irish Health Act of 2013 "specifically excludes biosimilars from the interchangeable list of small molecule chemical medicines and they cannot be substituted in pharmacies." Several member states prohibit substitution, while in Poland "there is no regulation against biosimilar substitution," and while France has recently legislated for biosimilar substitution under certain conditions, "due to legal issues, automatic substitution has not yet been implemented."

QUOTAS, GUIDELINES AND TENDERS

Another option for increasing the use of biosimilars is to set prescribing quotas for each physician or hospital, as happens in Germany and Italy, for example, the paper notes. Belgium has signed a contract to encourage use of biosimilars in at least 20% of new patients, while Sweden and the UK have financial rewards for physicians who meet quotas or targets.

There could also be a role for national, statutory or clinical prescribing guidelines for biosimilars, it says, noting that in the UK, the National Institute for Health and Care Excellence "provides guidance on options for using biosimilars, evaluation of biosimilars, licensing and comparability, pharmacovigilance, and brand name prescribing."

The consultation paper also asks respondents for their views on other approaches such as educational programs for physicians to increase their knowledge of, and confidence in, biosimilars, citing initiatives in countries like Belgium, France, Germany, Italy, Spain, Sweden and the UK.

> "A properly functioning and competitive biosimilar market in Ireland could have positive impacts across our health services"
> – Sandra Gannon, Medicines for Ireland

Other tools considered include gain-sharing deals such as the initiative at the University Hospital Southampton NHS Foundation Trust in the UK, where the savings from greater use of biosimilars are ploughed back into physicians' practices; and patient co-payment systems that favor cheaper drugs as in Spain, where patients must pay the full cost of the drug if the preferred medicine is not prescribed.

A further possibility, and one that is used in some other European countries, is to purchase biosimilars through tendering at national, regional or hospital level. The paper cites the well known case of Norway, where national-level tenders have produced price reductions of more than 70%, and notes that hospital-level tenders are also widely used in Belgium, France and Spain.

Poland uses exclusive tenders and "only the most cost-effective product, in terms of price, safety, effectiveness, sustainability and other factors, goes on the list of prescribable medicines," it says. "Norway and the UK use tenders where, for each drug class, the highest ranked medicine, in terms of cost-effectiveness, is the preferred drug to prescribe."

PRICING ISSUES

Many countries take the pricing approach: Germany, for example, uses internal reference pricing for biosimilars, and Greece makes use of external reference pricing, with biosimilars priced at the average of the three lowest prices across the EU. In Austria, the paper says, generic pricing policy is applied to biosimilars, "which means the first biosimilar on the market is priced at 52% of the reference product, the second biosimilar at 44% and the third at 40%."

In this respect, it is interesting that the government is asking respondents whether the price of the reference drug should automatically be reduced when it loses exclusivity in Ireland – the very measure that was included in the pricing deal signed by the government and the originator industry body IPHA last year.

Under that deal, the price of the reference biologic must be reduced to 80% of the original ex-factory price when a biosimilar is marketed, and the company must also pay a rebate equal to 12.5% of the value of the product at the reduced price, which equates to a total discount of some 30%.

Medicines for Ireland described the discount as a "blocker clause" that it said "must be reviewed if biosimilars are ever to achieve real traction."

The association said that while it welcomed the consultation, meaningful action must follow if Irish patients are to have access to more affordable and equally effective biosimilar medicines. "Each day that our health service fails to tap into the opportunities afforded by more cost effective biosimilars means patients lose out," Gannon commented.

"A properly functioning and competitive biosimilar market in Ireland could have positive impacts across our health services," she said. "For example, the recent controversy over the funding of nine new medicines could have been avoided through savings from biosimilars."

The Health Services Executive has just agreed to fund the nine products, but only after a dispute between the HSE and the department of health was resolved. *(Also see "Delayed Medicines To Hit Irish Market, But Uncertainty Remains For Future" - Pink Sheet, 3 Aug, 2017.)*

From the editors of Scrip Regulatory Affairs. Published online August 11, 2017

More Questions As Biocon Pulls EU Filings For Two Biosimilars

ANJU GHANGURDE anju.ghangurde@informa.com

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Investors slammed **Biocon Ltd.** on Indian bourses after the firm and partner **Mylan NV** retracted applications for their biosimilar trastuzumab and pegfilgrastim in the EU in the backdrop of manufacturing compliance lapses, though Biocon has underscored that it was only following the requisite regulatory procedure.

A pre-approval inspection by the French regulator, ANSM, had earlier flagged compliance deficiencies at Biocon's Bommasandra site in Bangalore for three biosimilars – pegfilgrastim, trastuzumab and insulin glargine and the Indian firm had, at the time, indicated that it would require a re-inspection of the "drug product" facility. The firm's "drug substance" facility had received good manufacturing practice (GMP) approval for both trastuzumab and pegfilgrastim, it had clarified.

"The request for withdrawal of the dossiers and re-submission is part of EMA (European Medicines Agency) procedural requirements linked to this re-inspection and will be considered by the EMA's Committee for Medicinal Products of Human Use (CHMP)," Biocon informed the Bombay Stock Exchange Aug 16.

Details in the agenda of the CHMP written procedure Aug. 14-17, posted on the EMA website, refer to "withdrawal of initial marketing authorization application" for pegfilgrastim and trastuzumab by certain applicants but gave no specifics. In addition, details in the agenda also refer to a letter from a trastuzumab applicant dated July 28, 2017 requesting an "extension of clock stop to respond to the list of questions." The author of the letter was not disclosed.

The Bengaluru-based Biocon also clarified that it was "on track" to complete its corrective and preventive actions (CAPAs) by the end of this quarter.

"It is our intent to seek re-nspection and resubmission thereafter,"it added.

Investors, though, appeared nervous and sent the Biocon stock sliding to close at INR328.80 (-5.86%) on the BSE on Aug. 16.

SETBACK AND UNCERTAINTY

The ensuing reapplication and reinspection requirements for Biocon's trastuzumab, experts say, come with potentially blurred timelines and analysts referred to the build-up of competition likely to result.

Hristina Ivanova, analyst at Informa's Datamonitor Healthcare, said that the withdrawal of the trastuzumab application would set Biocon/Mylan back in the race to get the first trastuzumab biosimilar in the EU, as it is not clear when they would be able to re-submit with the EMA. Notably, though, the same molecule recently received the unanimous approval of an US FDA advisory panel.

"Given that the FDA and EMA are moving towards mutually recognizing each other's GMP pharmaceutical inspections, it will be interesting to see whether the EMA withdrawal would affect the FDA's decision for approval of Biocon/Mylan's trastuzumab. The FDA has already expressed concern over Biocon's plant for trastuzumab production," Ivanova told the Pink Sheet.

Biocon's management has, however, sought to delink the EMA and FDA approval processes for its biosimilars. Biocon's chair and managing director, Kiran Mazumdar-Shaw, was reported telling a television channel that the EMA and US FDA will do their own review processes.

An FDA audit had earlier identified 10 deviations at Biocon's Bangalore manufacturing site, following an inspection between May 25 and June 3. *(Also see "Will FDA GMP Observations Stall Biocon's Run?" - Pink Sheet, 7 Aug, 2017.)* The setback comes in the run up to the anticipated FDA action date for Biocon and partner Mylan's biosimilar trastuzumab on Sept. 3, clouding sentiment and potentially commercialization timelines for products from the site if things don't settle without much delay; the user fee goal date for the duo's pegfilgrastim is Oct. 9.

COMPETITION BUILDS FOR TRASTUZUMAB

The latest EU filings retraction comes amid growing competition in the biosimilar Herceptin (trastuzumab) space.

Ivanova noted the emergence of a fifth "mystery" biosimilar trastuzumab filing with the EMA as of Aug. 4, according to the latest EMA list of applications for new human medicines under evaluation by the CHMP.

"So far, Biocon/Mylan, Celltrion, **Amgen Inc.** and **Samsung Bioepis Co. Ltd.** have announced filings; the fifth one is most likely Pfizer as they have now completed Phase III development. There is, however, no official company statement yet," Ivanova added.

Last month **Celltrion Inc.** and **Teva Pharmaceutical Industries Ltd.** announced that the US FDA had accepted for review their Biologics License Application for CT-P6, a proposed monoclonal antibody (mAb) biosimilar to Herceptin. *(Also see "Celltrion's Herceptin Biosimilar One Step Closer To US FDA Approval" - Pink Sheet, 1 Aug, 2017.)*

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OTC Monograph User Fees Still On The Table, But Not In Legislation

MALCOLM SPICER malcolm.spicer@informa.com

FDA will not be able to implement its proposed OTC monograph reform and user fee rules on Oct. 1, the start of US federal fiscal year 2018, because those changes were contingent on Congress passing enabling legislation.

So far, such legislation has not made it beyond the discussion stage, either as an independent bill or as part of the FDA Reauthorization Act, which renewed existing pharmaceutical and medical device user fee programs for five years, starting in FY 2018. FDARA is awaiting presidential action. *(Also see "Implementing User Fees Should Be Lighter Lift For FDA This Time Around; Bill Heads To White House" - Pink Sheet, 3 Aug, 2017.)*

On Aug. 23, FDA officials will conduct a webinar to update industry stakeholders on progress in its initiative, launched a year ago, to improve and modernize its OTC monograph program. The update will include an explanation that, without the authoring legislation, proposed new performance goals and monograph procedures remain on hold.

FDA and the industry hold out hope, though, that Congress will pass a bill to change the monograph system from its currently gridlocked and under-funded program to one that allows FDA to make changes and additions to monographs through orders rather than public rulemakings; allows exclusivity periods for firms that conduct research to support those proposals; sets timelines for proposal reviews and decisions; and imposes a user fee schedule to support the agency's work.

"We continue to support OTC monograph reform and remain actively engaged with Congress, industry, and public health stakeholders on OTC monograph reform efforts," said an FDA spokeswoman in an email. "Congress will determine the timing of potential passage of monograph reform and monograph user fee legislation."

The hope of stakeholders is that passage will gain momentum during this year or the second year of the current session of Congress. Sens. Johnny Isakson, R-GA, and Bob Casey, D-PA, have championed the OTC changes, circulating discussion drafts for legislation that tracks the changes FDA proposed in its performance goals and procedures document. *(Also see "OTC Monograph User Fees Totaling $22m To $34m Floated In Senate Discussion Draft" - Pink Sheet, 19 May, 2017.)*

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> On Aug. 23, FDA officials will conduct a webinar to update industry stakeholders on progress in its initiative, launched a year ago, to improve and modernize its OTC monograph program.

Supporters were unable to tie the OTC measure in time for Congress' passage of FDARA; the Senate sent the legislation to the White House on Aug. 3 and President Trump is expected to sign it into law after returning from a vacation.

"Based on the timing on the Senate side and with the bill passed by the House again, they were only able to include the existing bills," said Marc Schloss, the Consumer Healthcare Products Association trade group's head of federal affairs.

"We're still very heartened and optimistic about the movement of monograph legislation," Schloss added in an interview.

FDA's proposed goals document also includes a schedule for developing and launching an information technology platform accessible to the industry and the public that will track progress on proposals and on the agency's reviews.

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

WEBINAR MUST GO ON

The webinar was planned to provide an update on FDA's progress to improve the program as well as the, FDA says. *(Also see "OTC Monograph User Fee Goals Document Beats Authorization To Finish Line" - Pink Sheet, 27 Jul, 2017.)* "The timing of the webinar is not related to the timing of the passage of FDARA," the spokeswoman said.

"FDA commonly updates stakeholders and the public on the elements of the performance goals and procedures for potential user fee programs, prior to passage of user fee legislation," she added.

However, not only does the document state the timelines and performance goals that depend on authorizing legislation, FDA officials on multiple occasions have said the monograph program is irreparable without user fees to support

the agency's work.

OTC drug manufacturers, too, acknowledge that monograph changes aren't tenable absent new legislated provisions. That view is underscored by the absence of requested monograph changes. No proposals for adding ingredients (aside from sunscreen ingredients) to a monograph or for allowing additional indications for those ingredients currently are pending with FDA.

"Does [continuing with the existing system] forestall introducing new ingredients in a meaningful way, does it forestall new combinations in a meaningful way, does it forestall really novel dosage forms? Yes, it does," said David Spangler, CHPA's senior vice president for policy and general counsel.

The proposed goals include exclusivity periods for monograph proposal sponsors as drug firms have argued that they are not incentivized to invest in the research because any firm authorized to make and market drugs can incorporate monograph changes into their portfolio immediately.

> No proposals for adding ingredients (aside from sunscreen ingredients) to a monograph or for allowing additional indications for those ingredients currently are pending with FDA.

Setting timelines and eliminating lengthy rulemaking processes from monograph changes likely are more important to the industry, though.

"The bigger impediment is the fact that it takes forever," Spangler said.

Meanwhile, consumers miss out on potential savings for health care costs because the monograph system is not generating additional self-care products.

"OTC monograph reform would spur innovation, providing consumers with a wider range of choices and adding greater competition to the existing marketplace," Spangler added in an email.

From the editors of the Tan Sheet. Published online August 11, 2017

FDA's NDA And BLA Approvals: Lynparza, Besponsa

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				
AstraZeneca	*Lynparza* (olaparib)	100 mg and150 mg tablet formulation of the PARP inhibitor for maintenance therapy for patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy and for treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.	S, 3	8/17/2017
New Biologics				
Pfizer	*Besponsa* (inotuzamab ozogamicin)	CD22-directed antibody-drug conjugate (ADC) for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).		8/17/2017

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

Perrigo's Outgoing CEO Advocates OTC Switches, Starting With Statins

MALCOLM SPICER malcolm.spicer@informa.com

Perrigo Co. PLC CEO John Hendrickson used the pulpit of what was likely his final earnings briefing at the helm of the OTC private label leader to urge FDA and manufacturers to make more Rx drug ingredients available nonprescription.

During Perrigo's second-quarter earnings briefing on Aug. 10, Hendrickson, who will resign from his post when a successor is appointed, recommended specifically that statins "belong over the counter" through Rx-to-OTC switches, potentially through behind-the-counter sales.

Perrigo CEO John Hendrickson says "some kind of pharmacy intervention could make" available nonprescription.

Three new drug applications to FDA for a statin OTC switch failed and a fourth proposal stalled before an NDA was submitted *(see box, p. 20)*. Hendrickson recommended that drug firms look at incorporating a requirement for pharmacists' intervention into an application to make a statin available nonprescription.

"I think some kind of pharmacy intervention could make them out over the counter, almost like a third class. Not quite there yet, but I think even those will evolve that way if you look over the next three or four years," he told analysts.

Erectile dysfunction ingredients also might have more chance for a switch with a behind-the-counter caveat in applications to FDA, the CEO added. "Will those come over by themselves? Will there have to be a pharmacist saying, 'hey, do you have a heart condition?' … Who knows what intervention there will be, but I believe that those kinds of categories that are pretty expensive categories on the RX side will continue to switch."

Perrigo has not been involved in proposing the types of switches Hendrickson discussed though it often follows up on switched products with private label brands. But the exec took the earnings call as an opportunity to talk expansively about current issues, touching on drug pricing as well.

Savings in health care from making drug ingredients available OTC are an incentive for working with FDA on switches, he said. Drug pricing "created this stir" for Congress, state governments and payoes, and "also creates an emphasis to say, 'how do we manage that cost?' You bring products over the counter."

"It really gets the FDA starting to think not just about getting products approved for an Rx market, but also which categories make sense to switch. How we put these in a consumer choice versus government or private pay? What do we need to do? So, I think that sentiment does play into, if there are products that are safe and effective, we should help drive those."

While FDA has recently issued a drug competition plan, much of the focus has been on a decision to prioritize review of Rx generic applications for reference products with two or fewer approved ANDAs. *(Also see "Drug Pricing: Could Expedited Review Of Competing Brands Create The Desired Pressure?" - Pink Sheet, 19 Jul, 2017.)*

In addition to recommending statins, Hendrickson said some currently Rx dermatology treatments "are natural products to switch." Though "not billion dollar categories," the products "are safe, effective, could be self-prescribed, could be over the counter." Additional migraine treatments "are also kind of key ones" that could be switched, he said.

PRIVATE LABEL NEXIUM NEXT

In the short-term, Perrigo plans a second-half launch of private label and store brand versions ofthe *Nexium 24HR* (esomeprazole/20 mg) proton pump inhibitor, which in 2014 became the last of the Rx PPI brands to become available OTC and launched with three-year market exclusivity due to clinical data required in its NDA. *(Also see "OTC Nexium 24HR Rides Blockbuster History Into Full Field Of Competitors" - Pink Sheet, 9 May, 2014.)*

However, while private label esomeprazole for frequent heartburn is a factor in Perrigo's forecast for $225m in new product sales for 2017, it will not be the only generic of OTC Nexium available, unlike most of the firm's launches. Perrigo's product will face competition from other private label providers at launch.

The forecast is "risk-adjusted," Hendrickson said. "We are not planning on being alone in that Nexium market."

Providing retailers and other businesses with private label or store brand versions of OTC switch brands accounts for the sharpest increases in Perrigo's revenues, but the firm also has a steady growth driver from general consumer interest in spending less for generic equivalents of most every nonprescription brand.

"I believe our US consumer health care business can grow through a number of avenues. One is we have the acceptance of store brands. You may have thought we hit a cliff [but] it continues to grow," Hendrickson said.

TRIMMING INTERNATIONAL SAILS EFFECTIVE

Rather than expansion, contraction drove some of Perrigo's encouraging consumer health business results. The firm said it sold the Russian division of its international OTC drug and nutritional products business, but did not disclose the buyer or financial terms.

The sale is the latest step in trimming the segment's footprint and cutting distribution and manufacturing costs since expanding

its consumer health operations into Europe with its 2015 acquisition of German firm **Omega Pharma NV** *(Also see "Perrigo Starts Branded Consumer Product Rescue Mission In Belgium" - Pink Sheet, 8 Dec, 2016.)*

Hendrickson cautioned, though, that net income growth from Perrigo's international consumer business remains a long-term goal.

"We're still on what I consider to be a broader strategy of enhancing that business. … This isn't a next-three-months thing. This will continue to evolve over the next couple years as we continue to enhance the margin," he said.

The Dublin-based firm reported net sales for its international consumer health business were $377m, a total around 4% higher than the year-ago quarter when excluding $39m in sales from European distribution businesses the firm has exited and $16m lost to currency exchange. Sales growth in Europe, where Perrigo markets branded and private label OTCs and nutritionals, was led by $19m in new product sales and higher net sales in the allergy, analgesic and cough/cold categories.

Net sales for Perrigo's consumer products Americas division, including Canada, Mexico and Central and South America as well as the US, grew 3% to $605m during the April-June period on higher sales in the smoking cessation and dermatologic categories and stronger performance in Mexico.

Perrigo, which maintains its primary operations in Allergan, Mich., said new product sales in the Americas were $13m, primarily on US sales of its generics of Flonase Allergy Relief (fluticasone/0.05mg/metered spray) and new nicotine replacement gum products.

The Rx business reported net sales in the April-June period were down 13% from the year-ago quarter to $240m. However, even though an activist investor-led bloc of board members is pushing to

SWITCH HITS, MISSES AND MAYBES

One of the most recent OTC switches FDA approved, and the first nonprescription acne treatment approved since FDA finalized its OTC monograph for the indication, was Galderma Laboratories L.P.'s *Differin Gel* 0.1% (adapalene). The first-in-class product got FDA's nod in June 2016 as a once-daily topical for treating acne in consumers 12 and up. *(Also see "Nestle's Prospects To Lead OTC Acne Market Gel With Differin Approval" - Pink Sheet, 14 Jul, 2016.)*

GlaxoSmithKline PLC in late 2016 received FDA approval for Flonase SensimistAllergy Relief, the first OTC fluticasone furoate product, in a 27.5mcg spray, with plans to build upon the success of the original Flonase OTC line and help counter private label competitive activity in the intranasal corticosteroid category. *(Also see "GSK Aims Flonase Sensimist To Counter Generic Nasal Allergy Competition" - Pink Sheet, 8 Feb, 2017.)*

Merck & Co. Inc.'s three NDAs to switch *Mevacor* (lovastatin), including one done in a partnership with **Johnson & Johnson**, were not approved by FDA and Pfizer pulled the plug on a potential NDA for an OTC dose of Lipitor (atorvastatin/10 mg) after an actual-use trial showed concerns about whether consumers could accurately self-select and safely use a statin, the same reasons the agency rejecting the three Mevacor switch NDAs. *(Also see "Light Still On For Switches After Pfizer Pulls Plug On OTC Lipitor" - Pink Sheet, 3 Aug, 2015.)*

Sanofi is developing a switch application for ED drug *Cialis* (tadalafil), on license from **Eli Lilly & Co.**, and **Pfizer Inc.** has acknowledged considering an NDA for an OTC version of *Viagra* (sildenafil). *(Also see "Cialis Or Viagra Switch? Sanofi Survey, Pfizer Help Wanted Ad Could Be Signs" - Pink Sheet, 18 Nov, 2016.)*

Hendrickson's suggestion of behind-the-counter caveats for some nonprescription switches isn't an approach that FDA or others in the OTC industry have supported. The agency acknowledges firms see barriers to switch and are skeptical of options to ensure safe use of their products can be ensured through innovations such as extra-label information, instructions or questions accessed online. However, since FDA began its Nonprescription Drug Safe Use Regulatory Expansion initiative in 2012 on potential changes in the application process so sponsors could propose novel switches, including ways to expand safe use communications beyond the drug facts label, agency officials have made clear they are not suggesting behind-the-counter distribution for some switches. *(Also see "FDA's OTC Naloxone Study Is A Starting Point For Other Switches, Not A Roadmap" - Pink Sheet, 16 May, 2017.)*

Still, the first nonprescription emergency contraceptive was approved after the sponsor voluntarily amended its NDA to require pharmacy-only distribution. That requirement as well as age restrictions later were lifted, but the sponsor's initiative to limit sales of the product, which was a highly controversial topic for FDA, to pharmacy-only provided the agency with an option for approving the switch while assuaging concerns about distribution of the levonorgestrel drug. *(Also see "FDA Drops Access Restrictions On Generic OTC Emergency Contraceptives" - Pink Sheet, 5 Mar, 2014.)*

divest the Rx business, analysts are encouraged that the segment is stabilizing despite the price erosion hammering the prescription generics sector and the firm says it is considering adding ingredients or businesses to its generic topicals lineup with bolt-on acquisitions.

Hendrickson, whose June announcement of leaving Perrigo came after the investors joined the board, said he is not reconsidering his decision to leave even though his argument to retain the Rx business was supported by the segment's 4% volume sales growth and $6m in new product sales in the second quarter *(see box)*.

Perrigo's overall results for the quarter were a $70m loss, down from a $534m loss a year ago, on an 8% dip in net sales to $1.2bn.

The firm raised its full-year adjusted diluted earnings per share guidance to a range of $4.45 to $4.70, up from $4.15 to $4.50 it forecast with its first-quarter results, reflecting its expectations for the second half and the loss of around 5 cents per share in the sale of its Rx active pharmaceutical ingredient business in Israel.

Investors showed the same buoyancy as analysts for Perrigo as the firm's share price increased 15.9% the same day to $76.84 in high volume trading, more than 10m shares. Still, the price is a long way from between $200 and $180 with **Mylan NV**'s tender pending in the second half of 2015. *(Also see "Perrigo's Return To OTC Roots Restoring Investor Confidence" - Pink Sheet, 1 May, 2017.)*

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Pooled Purchasing Is Poor Answer To Latin American Drug Pricing Worries, Says Industry

FRANCESCA BRUCE francesca.bruce@informa.com

Pooled procurement will not solve problems relating to access to innovative medicines in the Latin American countries that have pledged to use it to win lower prices for high cost drugs, PhRMA, the US pharmaceutical industry lobby group, said.

Members of the South American trade bloc, Mercosur, recently announced they would be working together to buy high cost medicines, such as **Alexion Pharmaceuticals Inc.**'s *Soliris* (eculizumab) for paroxysmal nocturnal hemoglobinuria and **Roche**'s oncology drugs *MabThera* (rituximab) and *Herceptin* (trastuzumab) and other monoclonal antibodies. *(Also see "South American Pricing Coalition Sets Sights On Alexion's Soliris and Monoclonal Antibodies" - Pink Sheet, 28 Jul, 2017.)*. Argentina, Brazil, Paraguay, Uruguay and Venezuela are all Mercosur member states, while associate countries include Chile, Bolivia, Peru, Bolivia, Ecuador and Suriname.

Joint procurement is attractive to payers for a number of reasons. Such strategies can strengthen the position of smaller markets, which have little clout in pricing negotiations, particularly with big companies. Joint negotiations also mean that countries can strengthen their position by pooling their expertise on negotiating and on the disease in question. In addition, working together can also make purchasing or procurement processes speedier and cheaper.

In response to the news from Mercosur, PhRMA warned that "ultimately, pooled procurement does not address the challenges MERCOSUR countries are trying to address." It advised that instead governments and the private sector must together tackle underlying problems that hamper access to medicines, including regulatory, infrastructure, financing, and supply chain problems.

The association conceded that pooled procurement could be "one of many tools" to access medicines in exceptional circumstances, for example, during a pandemic. However, it added that "broad or mandated use of pooled procurement can negatively impact the capacity to address the challenges faced by patients." For example, such strategies could limit the number of distributors in a region, which could lead to higher prices in the long-term. Furthermore, such arrangements can prevent companies from offering differential pricing. "This can result in poorer countries within a procurement group – and poorer


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"Broad or mandated use of pooled procurement can negatively impact the capacity to address the challenges faced by patients" - PhRMA

countries globally – paying more for medicines than they would otherwise," PhRMA told the *Pink Sheet*.

For its part, Roche says it recognizes that medicine pricing is a "critical topic" in Latin America. "Thus, we strongly believe that any cross-border collaboration on joint price negotiations should have clear objectives set up-front and aim for increased patient access to medicines," the Swiss firm told the *Pink Sheet*.

However, the company says "there is no one size fits all solution" to the problem. It believes that a country-by-country approach to price negotiations is the best way to find "locally relevant solutions" to improve access to medicines. "We believe that commitment from and collaboration between governments, healthcare professionals, patients, innovation-based companies like ours, and many others is essential," it said. The firm added that it is vital that today's actions do not compromise the firm's ability to develop innovative medicines for tomorrow. Roche said it would continue to work with partners to develop tailored access solutions that support healthcare systems, improve diagnosis, increase disease awareness, train professionals, and address affordability issues in Latin America.

Meanwhile, Alexion says it has not yet been approached by Mercosur with regard to the purchase of Soliris. It says it is "willing to discuss specific country or government needs."

Several initiatives exploring joint price negotiations, procurement and health technology appraisals are underway in Europe. *(Also see "Where Europe's 'BeNeLuxA' Joint Pricing Pilot May Have Gone Wrong" - Pink Sheet, 30 Jun, 2017.)(Also see "More European Countries Agree To Swap Pricing Info And Negotiate Prices" - Pink Sheet, 9 Aug, 2017.) (Also see "More European Countries Agree To Swap Pricing Info And Negotiate Prices" - Pink Sheet, 9 Aug, 2017.)*

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Korea's Reimbursement Steps Spark Drug Price Cut Concerns

JUNG WON SHIN jungwon.shin@informa.com

The South Korean government will beef up its national health insurance coverage ratio in a bid to sharply lower medical costs for the nation and protect low-income households from catastrophically high medical expenses.

The Ministry of Health and Welfare aims to raise the health insurance coverage ratio to 70% of all medical costs by 2022 and eventually to 80% in the longer-term, from an early 60% level at present, as the country hopes to hike the ratio to the levels of major countries.

The latest measure is the first major health care step released under the new Minister of Health and Welfare Park Neung-hoo who took charge in July. It has raised concerns in the industry of potentially sharp drug price cuts as the government indicated it will also come up with measures to reduce fiscal spending.

DIFFICULT TO LAUNCH ACROSS-THE-BOARD CUT?

South Korean analysts, however, noted that the government is unlikely to conduct a large-scale drug price cut in the near term as there haven't been any meaningful discussions around this recently. Besides, Korean drug prices are relatively lower than prices in major countries.

The country's drug prices have been steadily falling due to post-launch management, so it will be difficult for the government to launch an across-the-board drug price cut as it did in 2012.

As South Korea's health insurance benefits increase, the country's prescription drug market could grow, leading to revenue increase for the pharma industry, the analysts noted.

The government has decided to release the latest measure as the portion of health care costs covered by national health insurance has remained at around 62%-63% in the past 10 years despite continued efforts to raise health insurance benefits.

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The Ministry of Health and Welfare aims to raise the health insurance coverage ratio to 70% of all medical costs by 2022, from an early 60% level at present.

"South Korea has high proportion of non-reimbursement so the people are faced with sharply higher medical cost burden compared to the people in advanced countries," said the ministry in a statement.

Among OECD member countries, South Korea had the second highest household medical payment ratio of 36.8% in 2014, after 40.8% in Mexico. This was 1.9 times higher than the average ratio of 19.6% for OECD countries.

MORE DRUGS ELIGIBLE FOR REIMBURSEMENT

The latest measure seeks to completely reimburse medical costs, excluding the costs for beauty and cosmetic surgeries.

However, in case of drugs with relatively low therapeutic effects versus cost, the government will apply a "preliminary reimbursement" system which will entail different reimbursement ratios for individuals.

This also means more drugs will be eligible for reimbursement. The government will maintain the country's positive list system, in principle, to reimburse drugs that have superior efficacy versus price, but will also actively seek to reimburse non-reimbursed drugs in stages.

The government will flexibly ease the medical cost burden of patients for use of medicines that weren't reimbursed due to ambiguous therapeutic effects versus high drug prices.

It will initially expand reimbursement scope of the drugs that are reimbursed for limited applications, including indications and administration times.

For pricey novel drugs for serious diseases, the government will seek to reimburse them after preparing measures that can prevent weakening of price negotiations.

To implement the plan, the government expects to spend a total of KRW30.6tn ($26.7bn) from the latter half of this year to 2022, using accumulated reserves and state support for health insurance. Along with this, it will also need to raise health insurance premiums to a certain level, but it plans to minimize the nation's burden by maintaining the increase rate at the average hike rate of 3.2% in the past 10 years.

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FDA Proposes More Restrictive Expiration Dating For Repackaged Solid Oral Drugs

JOANNE EGLOVITCH joanne.eglovitch@informa.com

FDA has revised longstanding draft guidance on expiration dating for unit-dose-repackaged non-sterile solid oral drugs, shortening the proposed period these drugs can be used from one year to six months after they're repackaged. Periods exceeding six months would be allowed if certain conditions are met. The revisions conform to USP standards on dating non-sterile, unit-dose repackaged drugs.

This proposal was announced Aug. 8 in FDA's revised draft guidance for industry, "Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products." The guidance does not cover sterile, liquid or topical products, or any products repackaged by state-licensed pharmacies, federal facilities and outsourcing facilities. The revised guidance describes the conditions under which FDA will not enforce certain stability study requirements for repackaged drug products.

This action was taken in response to increasing demand for solid oral dosage form drug products repackaged into unit-dose containers in various health care settings, which hold a quantity of drug for administration as a single dose. The guidance states that "the increase in unit-dose repackaging has led to questions regarding stability studies and appropriate expiration dates for these repackaged products."

FDA's current good manufacturing practice regulations require that each drug product bear an expiration date determined by appropriate stability testing and that the date must be related to storage conditions stated on the labeling under section 211.137 of Title 21 of the Code of Federal Regulations. Samples used for stability testing must be in the same container-closure system as the marketed drug under 21 CFR 211.166 to ensure the drug product's safety and efficacy over its intended shelf life.

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FDA's action esponds to increasing demand for solid oral dosage form drug products repackaged into unit-dose containers in various health care settings.

The guidance puts the agency's enforcement stance on these GMP requirements in line with USP standards for expiration dating. USP General Chapter <1178> on good repackaging practices recommends that repackagers affix an expiration date not to exceed six months from the date of repackaging, or carry the manufacturer's expiration date, or to cut the expiration date for

repackaged doses to 25% of their remaining expiration, whichever is earlier.

FDA is proposing to shorten the expiration date from 12 months under the current policy to six months or 25% of the time remaining until the expiration date on the container of the original manufacturer's product, whichever is shorter, and if the following conditions are met:

- The unit dose container complies with Class A or Class B standards as described in USP General Chapter <671> Containers – Performance Testing;
- The unit-dose repacking container provides light protection equal to or greater than that of the drug product's original container closure system if the drug product is sensitive to light;
- The drug product's original container has not been opened before and the entire contents are repackaged in one operation;
- Repackaging and storage occur in an environment that is consistent with the conditions described in the original drug product's labeling; and
- The drug product's labeling does not caution against repackaging.

In the earlier guidance on expiration dating issued in May 2005, the agency had proposed to set the expiration date for nonsterile, unit-dose repackaged drugs to one year, which also aligned with USP standards at the time for beyond use dating for unit-dose repackaging by dispensers. *(Also see "FDA Extends Expiration Dating Of Repackaged Drugs To One Year" - Pink Sheet, 31 May, 2005.)*

FDA also proposes to permit the expiration date to exceed six months if the above-listed conditions are met and if repackagers have supportive data from appropriate studies using an adequate number of samples to demonstrate that the container closure system used for repackaging is at least as protective of the drug product as the original packaging.

Once the revised draft guidance is final, it will supersede Compliance Policy Guide 480.200 "Expiration Dating of Unit-Dose Repackaged Drugs" issued Feb. 1, 1984, and revised in March 1995.

FDA will consider comments received by Oct. 10 when crafting the guidance's final version. Submit comments online to Docket No. FDA-2017-D-0829 at regulations.gov.

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CLINICAL TRIALS

Clinical Data Forgers Face Harsh Punishment In China

BRIAN YANG brian.yang@informa.com

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There have been 1,323 total NDA withdrawals since July 2015, when CFDA kicked off a crackdown on widespread clinical data forgery.

China's high court, the People's Supreme Court, issued ON Aug. 14 a legal explanation on clinical data forgery, providing solid ground for drug regulators to enforce good clinical practice (GCP).

The explanation first deems clinical data forgery as a criminal offence, subject to punishment outlined by China's Criminal Law under the "intentionally providing fake documents."

Six behaviors are considered as "severe violations" subject to a maximum five-year jail sentence or detention and fine. These are:

1. Deliberately using false testing of drugs in non-clinical research or clinical trials;
2. Concealing serious adverse events related to drugs clinical trials;
3. Intentionally damaging original drug non-clinical or drug clinical trial data;
4. Fabricating animal testing, study subject information, test process

records, research data and other non-clinical or clinical trial data that affect drug safety, efficacy evaluation results;

5. Providing false evidence in the past two years, which has led to administrative penalties, but re-submitting false evidence during drugs and medical device registration processes;
6. Other severe cases.

The latest legal explanation is a step up from a previously issued one that considered data forgery as a criminal offense subject to a maximum three-year sentence. *(Also see "Fake Clinical Data No More: China To Criminalize Forgery" - Pink Sheet, 18 Apr, 2017.)*

SPONSOR'S RESPONSIBILITY

The legal explanation also outlines two potentially "no-fly zones" for clinical study sponsors.

1. Use of reports generated using fake drugs: "If a staff member of the study sponsor is deliberately using the non-clinical, clinical research report and related materials generated using false drugs to obtain the drug approval certificate, such a violator should be prosecuted and punished as production and sale of fake drugs."
2. Instructing CROs or clinical sites to provide false non-clinical or clinical reports or related materials: "A staff of the drug study sponsors instructs drug non-clinical or clinical trial institutions and CROs to provide research reports generated using false drugs or data, such violator should be prosecuted and punished along with clinical sites and CROs violators."

The Court considers the following two behaviors to qualify as the above-mentioned "instruction": 1) Knowing that an institution, organization does not have the appropriate conditions or ability but still commissioning it for non-clinical and clinical trials; and 2) the price paid is obviously abnormal from standard cost.

While employers of the violators could potentially face a fine, the violators directly responsible shall be convicted and punished, said the Court.

"The judicial interpretation provides a much more solid ground for the CFDA to enforce GCP requirements." Ropes & Gray's Shanghai-based partner Katherine Wang told the *Pink Sheet* in a written response.

"It also clarifies the application of law in relation to different types of stakeholders who may involve in data falsification. Notably, the liabilities of imprisonment are primarily borne by individuals, not their employers. In practice, it may not be easy to point to specific individuals as wrongdoers."

CFDA: READY FOR INSPECTION OR WITHDRAW

While the court system has the ruling power, China FDA may hold the key to decide which cases are severe and subject to prosecution, legal experts say.

Currently, the drug regulatory agency has resorted to inspections and requested study sponsors to withdraw or face rejections of their new drug applications if data forgery is discovered during the on-site inspections.

Now, the agency has more in its arsenal to enforce GCP, including the power to turn repeated or severe violators to the courts for prosecution.

"It (CFDA) will only be consulted by the courts or prosecutors when the question of data forgery is disputable. In practice, once the CFDA concludes any willful data integrity issues during its study site audits, it can turn the case to the responsible prosecutors for criminal investigation and prosecution." noted Wang.

Amid a push for more clinical studies and innovative drug R&D, the CFDA has emphasized on quality and clinical data integrity, essentially requiring all sponsors to get ready for an on-site inspection, or withdraw the application without punishment before the inspection begins.

In June alone, 106 drug makers withdrew 135 new drug applications, adding to 1,323 total NDA withdrawals since July 2015, when the agency kicked off a crackdown on widespread clinical data forgery.

To have a smoother drug registration process in China, drug makers need to proactively monitor and correct any wrongdoings by CROs, Wang recommended.

"I believe that study sponsors will need to enhance its oversight and quality control over CROs and other third parties. Otherwise, sponsors may be deemed accomplices of the criminal offense."

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Published online August 17, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
GlaxoSmithKline's zoster vaccine recombinant, adjuvanted	Vaccines and Related Biological Products	Sept. 13
Results from a clinical study of Purdue Pharma's *Butrans* (buprenorphine) transdermal system in patients ages 7-16 years old for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate	Anesthetic and Analgesic Drug Products/Drug Safety and Risk Management	Sept. 14
Pfizer's *Sutent* (sunitinib) for adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma following nephrectomy	Oncologic Drugs	Sept. 19

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LEADERSHIP
Phil Jarvis, Mike Ward

CORPORATE SALES
John Lucas, Elissa Langer

ADVERTISING
Christopher Keeling

DESIGN
Jean Marie Smith

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

CUSTOMER CARE
1-888-670-8900 or 1-908-547-2200
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Sponsorship and Table Booking Enquiries:
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