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First Draft FDA User Fee Bill Is Squeaky Clean

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Lawmakers began the US FDA user fee reauthorization legislative process with the clean bill many desire, although it likely will not end up that way.

The House Energy and Commerce and Senate Health, Education, Labor and Pensions committees jointly released the first discussion draft of user fee legislation on April 14. The highlight of note is the bill's minimalism: there are almost no additions to the basic language necessary to extend the prescription drug, generic drug, medical device and biosimilar user fee programs another five years. It hews closely to the agreements worked out by FDA and industry.

The only non-user fee language would reauthorize exclusivity related to drugs with single enantiomers, pediatric humanitarian device exemptions and device consortia, as well as the orphan grants program and critical path public-private partnerships.

The discussion draft numbers 34 pages. The previous user fee reauthorization was enacted as part of the 140-page FDA Safety and Innovation Act (FDASIA), which President Obama signed into law in 2012.

Typically, the user fee bill attracts additional FDA and other policy changes because it is considered must-pass legislation. Additions to FDASIA included creation of the popular breakthrough therapies program. *(Also see "Following Through On Breakthrough: What's Next For FDASIA Success?" - Pink Sheet, 28 May, 2015.)*

This discussion draft contains no similar additions, although lawmakers could wind up inserting changes into a final bill. Energy and Commerce Committee Chairman Rep. Greg Walden, R-Ore., indicated that he is open to other inclusions.

"I look forward to continued discussions with my colleagues in the House on other member priorities that could strengthen this important legislation," he said in a statement announcing the draft's release.

Still, a clean first draft may be intended to send a message to lawmakers that they should avoid bogging it down with amendments. They are racing the clock to finish it not only before the user fee programs expire on Oct. 1, but also to ensure FDA is not forced to begin contingency planning.

If the bill has not made significant progress by August, FDA may have to notify employees supported by user fee funding that they may lose their jobs if the bill is not enacted by Oct. 1. That move would be expected to hurt morale and potentially prompt other departures. *(Also see "FDA's No Comment On Budget Plans Leaves Awkward Void" - Pink Sheet, 23 Mar, 2017.)*

HELP Committee Chairman Sen. Lamar Alexander, R-Tenn., has said he would like the bill to go to the White House before Congress adjourns for its August recess. He also asked that amendments be bipartisan

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and germane.

Congress returns from its current recess in late April, allowing only three months to pass the legislation and potentially complete a conference committee. *(Also see "US FDA Might Face Funding Penalty For Missing User Fee Goals" - Pink Sheet, 4 Apr, 2017.)*

TRUMP'S BUDGET PROPOSAL NOT INCLUDED

The draft does not reflect President Trump's proposal to significantly increase user fee revenues above levels expected to be generated by the FDA/industry agreement.

Trump's proposal is contained in his budget blueprint for fiscal year 2018, which would be the first year under the new prescription drug, generic drug and biosimilar user fee agreements. *(Also see "Trump's Budget Outline Threatens User Fee Agreements" - Pink Sheet, 16 Mar, 2017.)*

The discussion draft includes the baseline amounts that were negotiated, suggesting that lawmakers are not taking Trump's blueprint too seriously, at least as it pertains to FDA.

Trump had used the increase in user fees to justify a reduction in budget authority. He also called for a cut in budget authority for the remainder of FY 2017, as well as a slow in hiring. *(Also see "US FDA Faces Hiring Slowdown, Funding Cuts In Trump's FY 17 Plan" - Pink Sheet, 28 Mar, 2017.)*

OTHER CANDIDATES FOR INCLUSION LATER

Also absent, but potentially in line for a spot in upcoming bill drafts, is a monetary claw-back provision that would penalize FDA should it not meet the goals in the various user fee agreements.

A way of bringing down the price of expensive drugs, also is expected to be a candidate for inclusion in the bill. *(Also see "FDA User Fee Hearing Hijacked By US Health Care Reform Arguments" - Pink Sheet, 21 Mar, 2017.)*

In addition, FDA Commissioner-nominee Scott Gottlieb, who may be confirmed as the bill is reaching its final stages, has discussed potential legislative changes to the rules for complex generics in order to help them reach the market faster. *(Also see "Complex Generics: Gottlieb Eyes FDA Policy Changes To Speed Approvals" - Pink Sheet, 5 Apr, 2017.)*

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PINK SHEET COVERAGE OF THE NEW USER FEE AGREEMENTS

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Brexit: UK Could Be Asked To Foot EMA Relocation Bill; Bidding Criteria Drafted

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The UK will be asked to cover all the costs related to the relocation of the European Medicines Agency from London to another EU member state as a result of Brexit, according to the European Commission's draft Brexit negotiating directives. In the meantime, the Commission is understood to have drafted the criteria that member states interested in hosting the EMA will need to meet, which could be sent out sometime in May.

As well as meeting legal and budgetary commitments and other obligations when it leaves the EU, the UK "should fully cover the specific costs related to the withdrawal process such as the relocation of the agencies or other Union bodies," the commission states. The UK's financial obligations to the EU should be paid in Euros rather than sterling, it adds.

The proposal is part of a "Non Paper on Key Elements Likely to Feature in the Draft Negotiating Directives" drawn up by the commission. These detailed directives will be adopted after broader political guidelines have been approved by the other 27 EU countries – these will be discussed at the April 29 meeting of the European Council, which represents EU heads of government and state.

The commission document came to light as the EU is preparing to launch the highly charged process of deciding where the EMA should be relocated – a matter that is also expected to be discussed at the council meeting. As many as 22 countries are thought to have expressed interest in hosting the EMA, although not all of them are likely to meet the "objective criteria" that candidate countries will have to fulfil if they are to be in the running.

The commission is understood to have now drafted the criteria and it seems they could be discussed at the council meeting and then communicated formally to the member states around the beginning of May. Interested countries would then be invited to put their case and explain how they meet the criteria, which are likely to include infrastructure issues such as air links, transport from the airport to the EMA, housing, and accommodation for thousands of visiting experts.

It's not clear how long countries would have to make their bid, but it has been suggested that it could be about a month, meaning a deadline of sometime around the beginning of June. After that, the council would need to assess the applications and come to a decision.

Speed is of the essence, because the EU will not want the decision-making process to get tangled up in the wider Brexit talks. The EU authorities have in fact made it clear that the decision on the EMA's new location will not form part of the Brexit negotiations, despite suggestions in some parts of the UK media that the government wants it included in the talks.

The commission's chief spokesman, Margaritis Schinas, said the decision on the location of both the EMA and the London-based European Banking Authority was a matter for the 27 other EU countries and was "not part of the Brexit negotiations." The only related issue that would be discussed in the negotiations was how to ensure a smooth transfer of the agencies to their new homes.

> Frontrunners to host EMA are understood to include Austria (Vienna), Denmark (Copenhagen), Italy (Milan), the Netherlands (Amsterdam) and Sweden (Stockholm).

An official close to the matter suggested that if the UK had decided it wanted to stay in the single market in some way, there might have been a chance for the EMA to remain in London. "But the EMA regulates medicines in the single market, so of course it cannot stay in London."

It is likely that only a handful of the almost two dozen countries that have expressed an interest in hosting the agency will be serious contenders. Frontrunners – i.e., those that would most likely meet the criteria – are understood to include Austria (Vienna), Denmark (Copenhagen), Italy (Milan), the Netherlands (Amsterdam) and Sweden (Stockholm).

POLITICKING?

There have been calls for politics to be kept out of the relocation decision-making process, although this is unlikely. The commission will not want the criteria to be too tough for fear of accusations that this would automatically exclude certain member states, but on the other hand they should not be too easy to meet otherwise the decision will be made more difficult. *(Also see "Politics Could Get In Way Of Quick Decision On New EMA Home" - Pink Sheet, 6 Apr, 2017.)*

There may also be pressure to award the agency to one of the newer member states from eastern Europe. The existing EU agencies were established before the accession of the eastern European countries and some are suggesting this would be an opportunity to bring them further into the EU fold. However, the official pointed out that this consideration would probably only come into play if those countries first met the objective criteria.

The location of the EMA after Brexit will also have a huge impact on the number of its staff who choose to relocate. The agency has already said it could lose up to 50% of its staff. The official speculated that this could be as high as 80% "if it ends up in a country where the staff don't want to go."

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Dr. Reddy's Defeat Of FCA Case Offers 'Guidepost' For Litigation After Escobar

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Drug manufacturers are beginning to benefit from the US Supreme Court's landmark 2016 Escobar decision, which limits circumstances in which companies can be found to have made false claims for government reimbursement. **Dr. Reddy's Laboratories Ltd.** is one of the first to score a victory in the wake of the ruling, as a court dismissed a False Claims Act suit alleging the company did not comply with laws requiring child-resistant packaging.

The Supreme Court's opinion in Universal Health Services Inc. v. United States ex rel. Escobar makes it tougher to prove the government would have refused to pay a claim if it had known the information that was allegedly omitted or misrepresented by the claimant.

"One could fairly say that it is the most significant False Claims Act case in the past 30 years," Robert Vogel, of Vogel, Slade & Goldstein, said during an April 4 Food and Drug Law Institute webinar. Vogel and Gibson, Dunn & Crutcher attorney Jonathan Phillips discussed the impact of the Escobar decision and recent developments in False Claims Act (FCA) cases.

In the most recent decision post-Escobar, the US District Court for the Eastern District of Pennsylvania granted Dr. Reddy's motion to dismiss an FCA suit for failing to disclose its lack of compliance with the Poison Prevention Packaging Act and the Consumer Product Safety Improvement Act. In its March 27 opinion in U.S. ex rel. Schimelpfenig v. Dr. Reddy's, the court stated that the plaintiffs failed to allege sufficient facts to establish Dr. Reddy's nondisclosure with the laws was material to the government's decision to pay reimbursements.

The relator's theory was that if a manufacturer violates a statute, its drugs are not safe and are therefore misbranded and the government can reject payment. "The court said this was way too speculative," Phillips said. "This is a guidepost for how courts are going to look at these cases going forward."

In an interview, Phillips said that in FCA cases claiming violations of the Food, Drug, and Cosmetic Act, showing a connection to payments and showing how a violation is material to payment will now be that much harder to establish. Prior to Escobar, he said, the government and relators would argue that merely having the option to decline payment constituted materiality.

REGULATIONS, REPRESENTATIONS & MATERIALITY

The Escobar case involved a teenage beneficiary of Massachusetts' Medicaid program who received treatment at a psychiatric facility that was unlicensed and unsupervised by professionals, in violation of Massachusetts regulations. She died after receiving treatment at the facility and her parents filed a qui tam suit under the False Claims Act alleging that the lack of compliance with state regulations governing staff qualification and supervision rendered claims for Medicaid payment for psychological services false since the provider implicitly represented that it complied with the rules of reimbursement when it knew that it did not.

A district court threw the case out, concluding that none of the regulations violated by the facility were a condition of payment. The US Court of Appeals for the First Circuit reversed, holding that every submission of a claim implicitly represents compliance with relevant regulations and that any undisclosed violation of a precondition of payment renders a claim false or fraudulent.

In its ruling in the case, the Supreme Court held that implied certification can be a basis for False Claims Act liability when two conditions are met: the claim does not merely request payment but also makes specific representations about the goods or services provided, and it meets the materiality test. A violation would be material if the misrepresented information is likely to affect the behavior of the recipient of the information or the defendant knew or had reason to know that it would determine the recipient's choice of action.

Phillips said that in cases post-Escobar, some courts are looking at the centrality of regulations at issue while many others are looking at the government's conduct when it becomes aware of the allegations and whether the knowledge could negate some part of the FCA case.

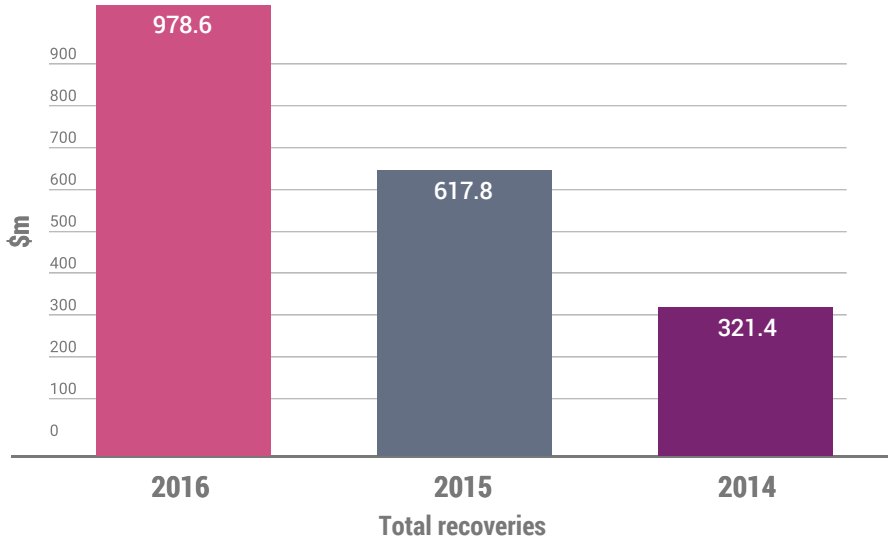
ONE BIG SETTLEMENT IN THREE YEARS

Pharmaceutical manufacturers face a constant stream of FCA complaints, in which a private individual, known as a relator, files suit on behalf of the government alleging fraudulent claims have been submitted for government payments. If the government intervenes in the case the relator receives a portion of any settlement. These complaints are known as qui tam suits.

Phillips, a former trial attorney in the Department of Justice's civil fraud section, noted that in 2016, FCA recoveries from drug and device companies totaled more than $1.4bn. Of this amount, $978.6m were recoveries from pharmaceutical companies, primarily from **Pfizer Inc.**'s $784.6m settlement with the DOJ. That case resolved allegations that the company's **Wyeth** subsidiary offered steep discounts to hospitals that purchased both its oral and IV *Protonix* (pantoprazole) acid suppressant drugs while reporting higher prices to the government. *(Also see "Pfizer Protonix Settlement May Deter Price Bundling" - Pink Sheet, 16 Feb, 2016.)*

The amount of FCA recoveries shot up 58% from 2015 to 2016 and 92% from 2014 to 2015. Gibson, Dunn's breakout of the figures according to theory of liability shows a rise in settlements involving

False Claim Act Recoveries From Drug Companies



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claims of violations of the anti-kickback statute and a decrease in those involving off-label promotion.

The Pfizer settlement was the second largest in the last four years after **Johnson & Johnson**'s $2.2bn settlement in 2013 over off-label marketing of *Risperdal* (risperidone). The size of DOJ resolutions has declined dramatically since 2012 when pharma companies were paying more than $1bn to resolve allegations of improper marketing of their products. *(Also see "Pharma Deals With The DOJ" - Pink Sheet, 14 Sep, 2016.)*

But the DOJ has not let up on pursuing these cases. Instead it has shifted its focus to pricing issues, issuing subpoenas to numerous companies for details about their patient assistance programs, contractual agreements with pharmacy benefit managers, support of non-profit organizations, and calculation of average manufacturer and best prices. *(Also see "Pharma Pricing, Non-Profit Ties Get Increasing Scrutiny From Prosecutors" - Pink Sheet, 14 Sep, 2016.)*

PHARMA VICTORIES IN KICKBACK, OFF-LABEL CASES

As for cases involving off-label promotion and kickback claims, the attorneys pointed to recent rulings for pharma companies. Pfizer and **Celgene Corp.** both won dismissal of suits alleging their speaker programs constituted kickbacks.

In a May 2016 opinion in U.S. ex rel. Booker v. Pfizer, the US District Court for the District of Massachusetts found that Pfizer's speaker series was under the safe harbor of personal services and there was no evidence that it was meant to compensate doctors for prescribing Pfizer drugs. The court also said that the fact Pfizer tracked its "return on investment" for the speaker series was unremarkable since only the attendees' prescriptions were tracked.

ANALYZE

Visit our website at http://bit.ly/2o8BG49 to access interactive data relating to kickback, off-label and improper billing cases.

And in U.S. ex rel. Brown v. Celgene, the US District Court for the Central District of California said in a Dec. 28 decision that Celgene's speaker program was unexceptional because its payments were not excessive compared to its peers. The court also rejected the claim that the speakers violated the anti-kickback statute by paying speakers to make drug recommendations to the audience. The court said that the statute was meant to cover recommendations to specific patients, not "generalized promotion."

However, the court declined to dismiss claims that Celgene promoted its multiple myeloma drugs *Thalomid* (thalidomide) and *Revlimid* (lenalidomide) for off-label use in cancer treatment. The court cited the company's promotional campaign prior to getting a cancer indication and the company's plans to provide reimbursement assistance to doctors.

Vogel said this case is exceptional as the marketing plan was to get the drug approved for narrower uses and then gear marketing to off-label use. He said the company has pressure to settle as it faces billions of dollars of potential exposure but that the plaintiff side also could have difficulty making its case.

Vogel and Phillips noted that pharma companies have won a string of victories in other off-label cases. Last year, the US Court of Appeals for the Second Circuit affirmed dismissal of claims that Pfizer improperly marketed *Lipitor* (atorvastatin) for use in patients whose cholesterol falls outside national guidelines. In U.S. ex rel. Polansky v. Pfizer, the court said "FDA does not prohibit physicians, who are free to do so, from prescribing Lipitor for patients with normal cholesterol" and it is thus unclear whom Pfizer could have caused to submit a false or fraudulent claim.

In another ruling in November, the First Circuit affirmed dismissal of claims that **Takeda Pharmaceutical Co. Ltd.** and **Eli Lilly & Co.** marketed the diabetes drug *Actos* (pioglitazone) for off-label treatment of prediabetes. The court found in U.S. ex rel. Lawton v. Takeda Pharmaceuticals that allegations of aggregate sales data for off-label prescriptions were insufficient and that the relator had to identify false claims, either individually or aggregated, from specific providers.

The First Circuit issued a similar opinion on Jan. 30 in U.S. ex rel. Booker v. Pfizer affirming the dismissal of claims Pfizer promoted the antipsychotic drug *Geodon* (ziprasidone) for off-label pediatric use. Phillips noted that the only evidence presented by relators was aggregate Medicaid reimbursement data for the alleged off-label use.

Vogel commented that the DOJ is cautious about intervening in off-label cases and looks for "off-label plus" conduct. The government is in a better position if it can allege the conduct was known to harm patients, or there is lying involved, he said.

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Times Have Changed: FDA Ends ESA REMS Ahead Of First Biosimilars

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FDA's decision to end the erythropoiesis-stimulating agent (ESA) class REMS is yet another symbolic milestone for the agency in moving beyond the drug safety debates of the 2000s – and also a timely step to help advance the emerging era of biosimilars.

FDA announced April 13 that it is releasing Amgen from its formal Risk-Evaluation and Mitigation Strategy obligations for the anti-anemia therapies darbepoetin (**Amgen Inc.**'s *Aranesp*) and epoetin (Amgen's *Epogen,* but marketed by **Johnson & Johnson** as *Procrit* for the oncology market).

The ESA REMS – which applied to oncologic indications for the anti-anemia agents – was one of the largest programs put in place by FDA in the period following the enactment of the 2007 FDA Amendments Act. It also almost immediately became a touchstone for the pushback from providers that has helped define the more recent and very restrained use of the FDAAA authorities.

The formal termination of the REMS is in line with a number of recent agency actions that close the books on high-profile drug safety controversies from a decade ago. But it is also timely in clearing out a potential obstacle for the launch of the new era of biosimilars.

Hospira Inc.'s pending biosimilar application for epoetin appears headed towards a near term FDA approval on its second go-around at the agency: FDA announced April 17 that it will be reviewed by the agency's Oncologic Drugs Advisory Committee on May 25. In general, FDA makes a policy of taking "first biosimilar" applications to committee prior to approval, as a public confidence-building exercise. That likely means that the application from the Pfizer Inc. unit would be approved by the agency ahead of its user fee goal date in June. *(Also see "Biosimilars In 2017: Crowded US FDA Review Queue, Key Legal Decisions" - Pink Sheet, 24 Jan, 2017.)*

Like the other approved biosimilars, there will still be a number of legal challenges ahead before the epoetin product can be launched in the US. However, by removing the ESA REMS obligation, FDA has eliminated any administrative headaches associated with trying to build a shared program for the biosimilar.

FDA's approval letter for the release of the REMS obligations indicates that the decision was originally made by FDA, and then the formal regulatory action came as an amendment to a pending supplement to revise the warnings on Amgen's ESA products.

"As communicated in the March 7, 2017 REMS Modification Notification Letter, we determined that the elements to assure safe use are no longer necessary to ensure the benefits of Aranesp (darbepoetin alfa) outweigh the risks and that the approved REMS for Aranesp (darbepoetin alfa) had to be modified to minimize the burden on the healthcare delivery system of complying with the REMS," FDA wrote. Amgen then amended its pending sBLA filings on March 17 to include elimination of the REMS, and the supplement was formally approved April 13.

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There is a much larger symbolism in the removal of the REMS that should not be overlooked in the context of the end of the product's exclusivity.

The reasons given for the REMS withdrawal by FDA come close to an acknowledgment that the program was unnecessary in the first place given changes in reimbursement policy that preceded the REMS. That in turn is likely to be a theme of FDA's approach to drug safety issues during the tenure of FDA Commissioner-nominee Scott Gottlieb.

A LANDMARK OF THE REMS ERA

FDA decision to impose the ESA REMS was a milestone event in 2008, when the class became the first major product group to have a risk management program mandated under FDAAA provisions that went into effect in March of that year. It also quickly became a case study in the complexity of implementing REMS.

First, from a regulatory process standpoint, it took two years from FDA's decision to order the REMS in April 2008 before the program was actually approved by the agency, and then another year before it was implemented in 2011. Almost immediately, the agency began to get pushback from providers concerned about the certification and registration process: despite the long run-up, there was very little prior appreciation in the oncology community of the burdens of complying with the program.

FDA's use of REMS has declined markedly over the years, and now the unwinding of the ESA REMS fits with a broader pattern of the agency revisiting and largely undoing some of the key actions of the "drug safety" era a decade ago. For instance, FDA formally released the *Avandia* REMS at the end of 2015. *(Also see "'Orphans' Hit Historic High At US FDA; More 'Me-Too' Drugs Urged" - Pink Sheet, 16 Dec, 2015.)*

The ESA REMS was imposed based on studies suggesting that routine use of ESAs in conjunction with myelosuppressive chemotherapy may actually be having a negative impact on treatment outcomes – perhaps due to a tumor-promoting effect of the ESAs.

However, the REMS itself came only after a prolonged period of safety scrutiny, including a formal relabeling by FDA intended to reinforce the agency's view that there was no data to support routine use of ESAs to reduce fatigue or for any other "quality of life" benefit, and that instead the indication was focused solely on reducing the risk of a blood transfusion. In addition, the Centers for Medicare and Medicaid Services instituted a new coverage policy to limit reimbursement for the therapies to patients where the risk of transfusion would be greatest. *(Also see "Living in a Bipolar World: Implications of the EPO Safety Debate (Part 1) " - Pink Sheet, 1 Jul, 2007.)*

FDA did not impose a REMS for the products in the dialysis setting, in part because the outcomes data in those patients appear to show clear benefits for routine use of ESAs. In addition, the dialysis payment system operates in a very different manner than the Part B physician payment system, and so there is less concern about potential incentives for overuse. *(Also see "FDA And ESA Safety: A Conversation With Bob Temple And Ellis Unger" - Pink Sheet, 31 May, 2010.)*

WAS THE REMS NECESSARY IN THE FIRST PLACE?

FDA said it made the determination to release the REMS "based on an evaluation of the results of the REMS Assessments submitted by Amgen, Inc., and additional FDA analyses to understand the impact of the various regulatory and other actions on the use of ESAs." Under terms of the REMS agreement, Amgen submitted annual assessments every February; the most recent submission reviewed by FDA was the February 2016 assessment.

Based on the sponsor's assessment, FDA concluded that "surveyed prescribers demonstrate acceptable knowledge of the product risks," and that "drug utilization data indicates appropriate prescribing of ESAs consistent with the intended use as a treatment alternative to RBC transfusion for anemia associated with myelosuppressive chemotherapy."

FDA's separate review of the utilization trends for ESAs from 2006-2014 essentially concluded that the market had already shifted to more appropriate use before the REMS was implemented in 2011.

"The FDA conducted an evaluation of the impact of multiple actions, including the ESA REMS, on the utilization of the ESAs using sponsor-submitted data from outpatient oncology practices between 2006 and 2014," FDA said. "During 2004-2009, the FDA took multiple regulatory actions, including labeling changes. In 2007, the Center for Medicare and Medicaid Services (CMS) made a National Coverage Determination (NCD) to limit coverage of ESAs for non-renal disease indications," the agency noted.

Collectively, those changes led to a decrease in use of ESAs overall, and an increase in the proportion of patients who appeared to be appropriate candidates for therapy (hemoglobin levels below 10g/dL) and who received doses "consistent with product prescribing information."

"Full implementation of the ESA REMS in 2011 had minimal impact on trends in these three ESA utilization metrics beyond the changes observed after the CMS coverage determination and multiple other FDA regulatory actions," FDA found. "This information led the FDA to conclude it is no longer necessary to require the certification of prescribers and hospitals that prescribe and/or dispense ESAs to patients with cancer in order to ensure the benefits outweigh the risks."

FDA goes on to note that the release of the REMS does not mean a change in view of the safety issue: "the serious risks of shortened overall survival and/or increased risk of tumor progression or recurrence associated with these drugs remain."

However, "the risks can be communicated by the current product prescribing information," FDA says. Moreover, "The appropriate use of ESAs is supported by the CMS NCD, the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) clinical guidelines which are evidence-based guidelines intended to provide a basis for the standard of care in clinical oncology."

THEMES TO CONTINUE UNDER GOTTLIEB

The decision to withdraw the REMS – and, more importantly, the justifications for doing so – are likely to resonate with the incoming Trump/Gottlieb FDA team. *(Also see "Gottlieb's Confirmation: He's Willing To Disagree With Trump, Sec. Price" - Pink Sheet, 5 Apr, 2017.)*

Gottlieb was a deputy commissioner at FDA when the ESA safety issues first arose, but left FDA before the FDAAA authorities took effect. After leaving the agency, he was critical of the early implementation of the REMS authority as infringing on the practice of medicine.

Gottlieb was asked about those views during his confirmation hearing in the Senate Health, Education, Labor & Pension Committee April 5. In an exchange about the agency's response to opioid abuse, Sen. Maggie Hassan (D-N.H.) cited an article published by Gottlieb in which he expressed concerns about the use of REMS. She wondered whether he would seek to roll-back FDA's program for prescription opioids.

Gottlieb first reassured Hassan that he supports the opioid REMS. In fact, in the article Hassan cited, "I affirmed…the use of trying to prevent diversion and abuse of opioid drugs" as consistent with FDA's mission and past practices, Gottlieb said. "I do fully support the use of that tool in this context," he added.

The commissioner nominee, however, also offered a broader message of support for FDA's recent, more-restrained use of REMS overall. The article, he told Hassan, "spoke to a different issue" that he sees as unrelated to the opioid crisis: the use of REMS "to attenuate the off-label prescribing" of drugs. "In fact, I support the use of the tool across a lot of contexts" beyond opioids, Gottlieb said. "The agency has gone on to use the program in ways that are more judicious than I was worried about when I wrote that article."

Gottlieb's past interest in FDA/CMS coordination – including his prior tenure at both agencies – is another theme underscored by the agency's rationale for dropping the REMS requirement. As commissioner, Gottlieb is likely to support the view that FDA can take a lighter touch on regulatory controls and defer to other entities – payers and medical societies/clinical practice standards – as better situated to optimize real world use of therapies. *(Also see "Drug Pricing Pundit Gottlieb Likely To Stay In His Lane At FDA" - Pink Sheet, 14 Apr, 2017.)*

From the editors of the RPM Report. Published online April 15, 2017

EMA Addresses Industry's Problems With Periodic Safety Update Reports

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The European Medicines Agency has issued additional guidance to address the challenges that drug companies have experienced in preparing their periodic safety update reports (PSURs) for evaluation under the EU's two-year old single assessment procedure.

The new guidance is in the form of an explanatory note to the EU's Good Pharmacovigilance Practices (GVP) Module VII. All marketing authorization holders (MAHs) should consult the explanatory note when preparing their PSURs, the EMA says. The agency has also released a Q&A document designed to guide assessors throughout the PSUR evaluation process.

The new guidance deals with issues that companies have raised since 2015, which is when EMA started evaluating PSURs under the periodic safety update single assessment (PSUSA) scheme. While it addresses specific challenges in the PSUSA for nationally authorized products, it also highlights issues that may apply to centrally authorized medicines.

PSURs evaluate the evolving benefit-risk balance of authorized medicines as evidence is gathered during their clinical use, and MAHs must submit these reports at defined points in time. EMA uses the information in PSURs to determine whether there are new or changed risks linked to a medicine, or if the balance of benefits and risks has changed.

Before 2015, PSURs for nationally authorized medicines containing the same active substance or the same combinations were submitted for assessment by their respective MAHs to different national competent authorities at different times.

In 2015, EMA began conducting single assessments of these PSURs in a bid to streamline the process and ensure that all the evidence generated about medicines containing the same active substance is reviewed at the same time by one authority, resulting in consistent safety information.

The PSURs are assessed by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), together with a lead assessor from one nominated national authority for medicines regulation, the so-called lead member state.

LIMITING REQUESTS FOR CLARIFICATION

The recommendations in the explanatory note are aimed at limiting the number of issues and requests for clarification that are raised during the assessment period, "given the time constraints of the procedure," the EMA says.

For example, the note advises the company's qualified person responsible for pharmacovigilance (QPPV) to ensure that PSURs "are prepared and written in a way that facilitates the understanding of the data, the conclusions and the subsequent actions, i.e., the logic flow needs to be clear and understandable."

New EMA guidance addresses challenges with preparing periodic safety update reports

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Regarding changes to therapeutic indications, it clarifies that a PRAC recommendation stating that the benefit/risk balance for certain indications authorized in only some EU member states remains unchanged cannot be used as the basis for an extension of indication in other member states where the indication is not authorized. Instead, applications for new indications need to be submitted via the appropriate regulatory procedure to the relevant national competent authority, including a comprehensive data package, it says.

The note states that if significant actions have been taken anywhere around the world for safety reasons in the reporting interval of a PSUR, they should be described in sufficient detail to allow the assessor to understand whether the safety reasons for the action(s) have any impact on the benefit-risk profile of the product. "For instance, simply stating 'interruption of the placing on the market' would not be considered as sufficiently informative."

It says that while it recognizes that it is often difficult to obtain and validate exposure data, the number of patients exposed to the drug should preferably be provided alongside the exposure length (preferably number of patients or patient/year). "The method should be explained. Where a discrepancy exists… this should be explained."

Discrepancies in the patient exposure reported from one PSUR to another (e.g., discrepancies between previous and current cumulative exposure, different units used or data missing) should be justified and elaborated upon with an adequate level of detail, the EMA says.

The explanatory note also deals with areas such as: how to prepare PSURs for generic drugs; reference product information; data in summary tabulations; provision of study reports; signal evaluation; late-breaking information; characterization of risks; benefit-risk analysis evaluation; assessment and outcome; and quality systems that MAHs should use for PSURs.

The ultimate plan is for the explanatory note to form the basis of the upcoming revision of GVP Module VII. The EMA is also planning to organize joint training in the second quarter of 2017 for industry and EU national competent authorities to support the implementation of the optimized single assessment process.

From the editors of Scrip Regulatory Affairs. Published online April 14, 2017

Brazil Patent Agreement Hopes To Increase Flow Of Generics To Market

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In an effort to bring more predictability to the pharmaceutical patent application process and spur a flow of generics to market, Brazil's National Sanitary Surveillance Agency (Anvisa) and the National Institute of Industrial Property (INPI) have signed a joint ordinance that clearly defines the role of each agency in the process.

Under the agreement – signed April 12 by Anvisa Director Jarbas Barbosa da Silva Júnior and INPI President Luiz Otávio Pimentel – Anvisa's role in the patent process will be limited to the analysis of public health matters, such as whether the application covers a substance that is prohibited in Brazil. INPI will be responsible for analyzing the patentability criteria.

If Anvisa determines that the product in question is of strategic value to Brazil's public health system, it may issue a patentability opinion to INPI based on aspects such as novelty and inventive activity. The final decision, however, will lie in the hands of INPI.

"We will give predictability in what is clearly provided in the law, thus avoiding the extension of the patent process," Barbosa da Silva said. "The measure aims to expand the development of generics in Brazil. The intention is to generate more savings for the [Unified Health System] and for the population."

Anvisa's role in the patent process will be limited to the analysis of public health matters. INPI will be responsible for analyzing the patentability criteria.

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HOW THE PROBLEM STARTED

Enacted in 2001, Brazil's Law 10,196, which outlines the course of action of patents in South America's most populous country, stated that any pharmaceutical patent application submitted to prior consent of Anvisa, rather than being exclusively prosecuted at INPI.

"The agency used to understand that it would have the right at least sometimes to review patentability criteria in patent applications as a condition for giving or denying prior consent," the Brazilian intellectual property law firm Dannemann, Siemsen, Bigler & Ipanema Moreira said in a note. "This created an impasse between Anvisa and INPI, since it resulted in the prosecution of patent applications not accepted by the Agency due to patentability objections simply being frozen."

The result was 16-year impasse between the two agencies in area of pharmaceutical patent applications.

Consequently, lags in the patent process allowed patent holders gain extra time in addition to the minimum 10-year term. A study by the Institute of Economics at the Federal University of Rio de Janeiro found that patent holders could gain between 1.75 and 5.58 additional years in addition to the legal deadline because of delays.

Patents have long been an issue for innovators in Brazil. It can take up 14 years to obtain patent approval, as there have been several management issues in the government on the subject. *(Also see "Biodiversity Law Reform Spurs Innovation, But Patent Backlog Remains" - Pink Sheet, 31 Oct, 2016.)*

The Brazilian government did not allow drugs and biotechnology products to be patented until 1996, and the change in law resulted in an influx of patent applications – and produced a massive application backlog. Excessive bureaucracy, a lack of sufficient patent examiners and political turmoil have also been contributing factors to the backlog.

A WIN FOR GENERIC SPONSORS, INNOVATORS TOO?

Barbosa da Silva says in addition to bringing predictability to the process for generic developers, it will also help the country's national health system save money with an increase in cheaper alternatives on the market. He added that innovators will also have more security under the agreement.

"The joint order closes any conflicts of jurisdiction between the two bodies in relation to prior consent in the patent granting procedures, thus eliminating differences in the interpretation of the legislation on the criteria for analysis," Anvisa says in a state-

ment. "For the chemical-pharmaceutical sector, the ordinance reduces bureaucracy and improves the business environment by offering legal certainty and agility in the examination of orders."

The Pharmaceutical Research and Manufacturers of America told the Pink Sheet that the ordinance "is an important first step in granting effective patent protection."

"In the last few years because of the conflict between ANVISA and INPI the granting of patents was stalled," a PhRMA spokesman said. "We are hopeful that the delays in issuing patents will now decrease. More importantly, the agreement establishes INPI as the only public entity able to decide patentability criteria."

WHAT ELSE IS IN THE ORDINANCE?

The rule will be applied to pending patent applications that have already been examined by Anvisa. According to the drug regulator, there have been 21,733 patent applications for pharmaceutical products between 2000 and 2015 submitted to INPI.

If Anvisa denies prior consent to a patent application, the application will be sent to INPI, which will withdraw the patent indefinitely and publish the withdrawal in Brazil's *Industrial Property Journal* (RPI).

In the case where Anvisa determines the drug is of strategic value to Brazil's health system, and issues a patentability opinion to INPI, INPI must also publish the opinion of Anvisa in RPI. INPI must provide a written opinion citing technical grounds if it does not agree with Anvisa's opinion.

The ordinance further establishes an Interinstitutional Working Group, which will be established "with the participation of representatives from INPI and ANVISA, focused on providing a broad exchange of technical information and on harmonizing understandings.

The ordinance takes effect 60 days following the April 13 publication of the rule.

WILL IT WORK IN PRACTICE?

Despite the optimism expressed by Anvisa, the Brazilian legal community says only time will tell in assessing how the ordinance translates in practice.

"We will have to wait and see how this will work out," Marcos Levy, a senior partner at the Brazil-based law firm A. Lopes Muniz Advogados Associados, tells the Pink Sheet.

Levy referred to the conflict between Anvisa and INPI as "a long and insane dispute."

In 2010, Levy had written, "It is odd, to say the least, that a governmental agency, linked to the Ministry of Health, responsible for sanitary surveillance, which is what ANVISA is, is given an attribution that is the competence of a different institution, in this case the INPI, linked to the Ministry of Development, Industry and Commerce," in an article for executiveview.com.

Dannemann, Siemsen, Bigler & Ipanema Moreira also expressed caution about the ordinance. The law firm noted that the measures "aim at finally solving the above conflict and polemic," but added that "It will be necessary to wait in order to see how INPI and ANVISA will execute this rule in practice."

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Can Big Data Match Up To The Big Promise?

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Digital technology is allowing the generation of increasingly large amounts of health and other data from digital sources such as electronic health records, mobile apps and biological analysis that could be used to support and improve both drug development and regulatory decision-making.

But while "big data" brings many opportunities, it presents challenges too: how to integrate disparate datasets and ensure that the resulting knowledge can be trusted and used for the intended purpose, for example, and how to find a balance between individuals' right to privacy and the use of personal data for the greater good.

These and other aspects of the "digital revolution" in healthcare were debated during a session at the recent DIA EuroMeeting in Glasgow, UK, where panelists from industry and the regulatory arena examined current approaches to data management and likely developments in the pharmaceutical area in the short and long term.

For Alison Cave, principal scientific administrator at the European Medicines Agency, the most exciting prospect from a regulatory point of view was the ability in future to capture a "holistic picture of the patient, not just a snapshot from the clinical visit but a longitudi-

nal capture of information across time." This would allow information to be gathered on "social behavior and environment factors that we can't get any sort of handle on now but we know will affect the way the patient reacts to a medicine and the benefit-risk profile."

This, she said, gave a glimpse of how patients and diseases could be better stratified in future, how information could be made more accessible and searchable, and how duplication could be prevented.

> Some companies had tried to bring data together but had hit a "roadblock" in regulatory terms. – James Streeter, Oracle Health Sciences

But there were "huge" challenges ahead, not least in how to handle and use the vast amounts of data coming from very difference sources, such as the 165,000-odd mobile apps now on the market, said Cave, who co-chairs the EMA's recently established big data task force. *(Also see "Denmark Leads New EU Task Force Exploring Use Of Big Data In Medicines Assessment" - Pink Sheet, 23 Mar, 2017.)*

"The volume of data and the speed of accumulation of data are a real challenge," she said. "How can we validate that information in a sensible way so that as regulators we can make decisions on that data?"

A key issue, she said, was how to integrate information from across different types of datasets. The question was also addressed by James Streeter, vice-president, life sciences product strategy, at Oracle Health Sciences, who said it was vital to understand how to structure the available data and bring it together in a usable form. "You can't just take several datasets and bring them together without knowing how to attach them. We need to know the quality and the usefulness of the data."

He suggested that the regulators and legislators had a role to play in this respect, remarking that some companies had tried to bring data together but had hit a "roadblock" in regulatory terms. "They really put walls up, and don't allow us to bring data together that's needed, whether in healthcare or life sciences, so that we can really take technology to the next step," he declared.

HOW TO USE THE DATA

The benefits of large amounts of data will only become apparent if the data are meaningful and if we trust the evidence generated from it, Cave said. "We talk a lot about real world evidence but the evidence is derived from the data and we are still working on it" and trying to understand issues like biases and confounding factors. "We need to build that confidence, understand what works and doesn't work, and we need to be working in a transparent way."

Early interaction and understanding the processes used to generate the evidence will be vital. "Over time we can document that and start to develop guidelines on what is acceptable and what is not, and that acceptability will depend on where the evidence is being used," Cave said – whether it is used to support marketing authorization, provide evidence on potential adverse drug reactions, and so on.

In this context, Jospeh Scheeren, senior vice-president and head of regulatory affairs at Bayer Consumer Care, noted that the US Federal Big Data R&D Strategy Plan – which began in March 2012 and was made public in May 2016 – involves seven strategies to "bring the US to the next level on the use of big data."

These include the leveraging of big data techniques and technologies, the trustworthiness of data and the resulting knowledge, fostering databases, training people able to deal with new kinds of data, and data collection and sharing.

"All these topics are very important," Scheeren said, noting that his company was working on artificial intelligence and machine learning, as well as education and training, developing different skill sets to allow people to "meet the changes that are coming."

REAL WORLD DATA

A key question nowadays is the utility of real world data (RWD), particularly the extent to which it can be substituted for randomized clinical trials (RCTs). Patient registries containing RWD, said Cave, can be "incredibly useful sources of information" in terms of supplementing data from RCTs.

The RCT still remains "the central source of data for decision making," but RWD has "multiple opportunities to complement that data source to give us additional information," Cave noted. This could be, for example, extra data on pediatric or geriatric patients, or, in the post-authorization phase, allowing the proactive capturing of information on the long-term benefit-risk profile of a medicine.

Asked how often digital data had influenced regulatory decisions, Cave said it depended on the point in the product's life cycle. Data are being used, for example, to generate information about disease progression, stratification of the disease and the patient population, the optimal therapeutic window, and potentially the use of surrogate endpoints in clinical trials.

She also pointed out that all data sources have their strengths and weaknesses, saying "I think it is important for us to understand these so we can understand which questions we can ask of which data source" and which information is required.

"We have substantial experience but we are now looking for more opportunities to use this data to complement data that is coming in at the pre-authorization stage, but again I would say that we need a clear understanding of different data sources and strengths and limitations, and the context of where the data is going to be used in the product life cycle."

To industry members of the audience, she said "we would definitely encourage engagement with formal processes of how you come and talk to the EMA, and start to build knowledge of what is and isn't acceptable" in terms of data.

As for the key future opportunities in this area, she said that the "low-hanging fruit" was probably RWD, but better use could also be made of clinical trial data. There were "huge amounts of data locked away," and now "we are beginning to develop platforms where we can access that data," she said. "We have examples of where that data has been mined and we can get much better information around pa-

> "I see huge value in these registries and ... I would love these registries to be able to talk to each other so that we can get bigger datasets and analyze them. This would be hugely beneficial, it just needs to happen in a safe environment." – David Haerry

tient stratification and disease progression, and develop biomarkers that predict the course of disease in different patients."

Then there was "the far future": integrating multiple types of data – genomic, proteomic, metabolomic data sets – with clinical data and understanding where the linkages and associations are. But Cave said that was "really challenging because you don't want to make spurious associations." Validating those associations would be difficult and would take time, "but as we build our experience that's where we may derive the deepest insights," she declared.

DATA ACCESS AND PRIVACY

Data access and data privacy – including the patient's trust in how their data are being used – are other key challenges, according to Cave. "We are going some way to addressing the issue of privacy and trust in data with the [EU] General Data Protection Regulation" that comes into effect in May 2018, she said. The regulation introduces the concept of accountability for all organizations that make use of personal data, and says that "data protection should be by design, not default, so it should be built into all our processes right from the beginning," she observed.

The question of data protection was also addressed by David Haerry of the European AIDS Treatment Group based in Belgium, who said he was concerned about issues like information from smartphones, the digitalization of healthcare, the safety of handling of genomic data, and the lack of legislation and governance on biobanks.

"We don't know what these people are doing with our data, and we see companies exploiting this data. I would like the patient to be the owner of the data and decide who should use it. It should be to the benefit of society."

He said that as an HIV patient he had experienced the "deep impact" the availability of such data had on his treatment and quality of care he had received from the HIV patient registry in Belgium. "I see huge value in these registries and I would love every indication to have one, and I would love every country to have one, and I would love these registries to be able to talk to each other so that we can get bigger datasets and analyze them. This would be hugely beneficial, it just needs to happen in a safe environment."

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Fake Clinical Data No More: China To Criminalize Forgery

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In a document issued April 10, China's top court, the Supreme People's Court, has said it is planning to make clinical data forgery and similar violations criminal acts subject to formal legal punishment.

The court listed three categories of behavior that will be considered criminal under the proposed changes:

1. the intentional submission of fake non-clinical and clinical research reports by non-clinical trial sites, drug and medical device clinical sites, and contract research organizations (CROs), which will be punishable under document forgery charges;
2. drug product sponsors using fake data, and filing untrue non-clinical or clinical data and materials to gain product approvals, which will be subject to be charges of manufacturing and selling fake products; and
3. the collaboration of non-clinical sites, drug and device clinical sites, and CROs with sponsors to provide fake data and materials for the purpose of product approvals, which will be considered as both document forgery and the manufacture and sale of fake products, with heftier punishments.

The explanation document that has cleared the court will be officially released after sign off by the People's Supreme Procuratorate. The court said it had started drafting the explanation document in July 2016 and had held discussions with the prosecutor's division, Public Security Ministry, and China FDA.

TOUGHER MEASURES

According to China's current Criminal Law, violators found guilty of document forgery are subject to a maximum three-year prison sentence or detention, potentially combined with a fine. Meanwhile, manufacturing and selling fake drugs is subject to three years in prison or detention, with a fine.

The crackdown on clinical data forgery specifically comes as the government has vowed to root out data integrity violations for drug and medical device registration purposes. The CFDA has said generally it is aiming for the highest standards, strictest enforcement, and severe punishments to ensure the safety of such products.

Existing problems with the veracity of data in product approval applications led the national drug review agency to launch a full-fledged crackdown on clinical data violations last year, which led to the withdrawal of nearly 80% of the 1,622 new drug applications singled out for official attention.

CFDA JUDGEMENT KEY?

Legal experts say that while the newly released court document provides more details on the planned new punishments for clinical data violations, the CFDA will play a vital role in judging whether a certain case is actually criminal or not.

"The new document is to fill the current loopholes when it comes to enforcement," Chen Yang, partner at law firm Sidley & Austin in China, told Pink Sheet. "Although previously there was a blacklist for violators, and measures including withdrawal of new drug applications, there lacked detailed punishment for severe violators."

However, the criteria for judging a case that is severe enough for criminal prosecution are still unclear, noted the lawyer. The CFDA as an administrative branch is thus expected to hold the key to deciding whether to transfer a case to investigative agencies for further prosecution.

Existing problems with the veracity of data in product approval led to the withdrawal of nearly 80% of the 1,622 new drug applications singled out for official attention.

"It depends on how much CFDA knows about the violations, as the agency must make the decision to transfer a case," Yang said.

The real potential impact, other legal experts say, could be a strong warning to those planning clinical data violations. "The current document should be released as it is," suggested Katherine Wang, a partner at Ropes & Gray in China. "It fits the CFDA's emphasis on clinical data integrity."

Wang added that "CFDA's administrative decision can provide a foundation for an ultimate legal ruling. "Although courts make the final judgement, CFDA's narrative of a clinical data forgery case will have a decisive impact, and courts [will] then decide on the degree of penalty based on intention and other evidence."

From the editors of PharmAsia News. Published online April 18, 2017

FDA's NDA And BLA Approvals: Clindamycin

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				
Celerity	Clindamycin in 0.9% sodium chloride	300 mg/50 mL, 600 mg/50 mL and 900/50 mL intravenous/ injectable formulation of the antibacterial to treat serious infections caused by susceptible anaerobic bacteria; infections due to susceptible strains of Streptococci, Pneumococci and Staphylococci; lower respiratory tract infections; skin and skin structure infections; gynecological infections, intra-abdominal infections; septicemia; and bone and joint infections.	S, 5	4/20/2017

KEY TO ABBREVIATIONS

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

Tylenol Delivers J&J Relief As Global 'Consumer Staples' Sales Slump

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Johnson & Johnsonsays *Tylenol* products were a bright spot for its consumer health segment in the first quarter as a "global category slowdown" makes an impact across the overall consumer products spectrum.

Global OTC drug business sales grew 1.4% on a reported basis to $1.01bn, the firm said April 18. US sales for the segment advanced 2.4% to $477m and international sales were flat at $536m, up 0.6%.

J&J's overall consumer health segment sales in the January-March period reached $3.22bn, up a reported 1%, domestic sales advanced 4.1% to $1.41bn and international sales slipped 1.3% to $1.81bn.

J&J reported overall net income of $4.4bn, or $1.61 per share, down from $4.5bn, $1.59 per share, in the year-ago quarter. Revenue totaled $17.8bn, up 1.6% but below consensus forecasts of $18bn.

Read the full article here

Spokesman Joseph Wolk said the same "overarching theme" is influencing J&J's business and other consumer product firms, both within and outside the pharma industry: first-quarter results "negatively impacted by global category slowdown."

Wolk, recently named investor relations vice president after longtime VP Louise Mehrotra's retirement, said consumer product market analysts' research and "peer commentary" published recently are "highlighting higher gas prices, retailers reducing inventory levels and delayed tax refunds among many factors for slower growth."

For instance, a Zacks Equity Research March 29 analysts' blog acknowledged the consumer staples sector has been weak "for quite some time now," making investors skeptical. "Headwinds like unfavorable currency, food deflation, declining volumes, potential price wars, a competitive environment, slowdown in international markets and other global issues have been plaguing the companies

in the sector," Zack's analysts said.

Nevertheless, J&J could count on the venerable Tylenol brand for a silver lining to the consumer segment dark cloud. Sales of adult and children's Tylenol products were ahead of other products in the categories and adult Tylenol has climbed to the No. 2 selling branded ibuprofen analgesic, Wolk said.

In January, the New Brunswick, N.J.-based firm reported its analgesics segment was back on track after the firm remediated its three manufacturing sites impacted by a consent decree with FDA following good manufacturing practice problems. The firm reported it had returned all recalled product lines to store shelves and the OTC unit sales grew 2.1% in 2016 $3.98bn. *(Also see "J&J Promotes Preventive Care, Wellness In US Health Debate" - Pink Sheet, 26 Jan, 2017.)*

J&J CONFIDENT IN RETAILER INVENTORIES ...

Still, analysts suggested J&J and other consumer product firms could be slowed by retailers spending less on inventories with consumer spending slowing.

Retailers' deceleration in product stocking, though, is "a phenomenon that we think is not long-lived," said J&J Chief Financial Officer Dominic Caruso. "Obviously, eventually as consumption either picks up or even continues at a reasonable pace, inventory will need to be restocked at the trades. So we'll see some correction to that," Caruso said.

He added that product launches, including some in the first quarter, are expected to generate around 2 points of incremental growth for J&J's consumer business in 2017. (J&J declined to comment on details about product launches.)

The products "could impact our total growth rate by an incremental two points of growth going forward. So we don't think that the first quarter results for consumer will continue at the pace that we just saw. We think they'll improve throughout the year," Caruso said.

The CFO also noted "many industry reports" suggest the consumer health care category will rebound in the near-term and J&J expects to be "well-positioned to grow above market through geographic expansion of current products."

In a same-day report, Morningstar Equity Research analyst Damien Conover also anticipates a rosier outlook for J&J's consumer group – close to 3% growth annually over the next three years.

"While the consumer group posted growth below this longer term view in the quarter, due partly to competitive pressures, we believe the brand power and entrenched products should return to a more normalized growth rate in the remainder of the year."

... SEES NO E-COMMERCE MARKET SHARE THREAT

Caruso also dismissed analysts' concern that "accelerating e-commerce" will take market share from J&J's consumer health brands to competing products. The firm has its own online sales footprint as well as its presence on store shelves, he said.

"Our brands are iconic in nature. They do still have quite an appeal to a mass audience, and you see us continuing to advertise, for example, in *Neutrogena* and *Aveeno* and Tylenol. So we think those brands still hold up well in more classic

marketing, although we're very present in e-commerce," he said.

J&J made e-commerce one of its strategic 'how-to-win" priorities to strengthen its go-to-market and commercial capabilities following the FDA consent decree. *(Also see "Expanding $1 Billion Brand Club Fits In J&J Consumer Big Picture" - Pink Sheet, 4 Apr, 2016.)*

Like J&J, OTC drug and personal care product firms **Procter & Gamble Co.**and **Colgate-Palmolive Co.** have committed to e-commerce strategies but plan to keep their primary focus on traditional sales platforms.

P&G, which markets *Prilosec OTC* heartburn medication and *Vicks* cough and cold products, in 2016 said it would continue its direct-to-consumer business, which consists of P&G Shop and subscription-based businesses for men's grooming, but would keep its focus on conventional sales. *(Also see "Colgate Builds On Oral Care, Counts E-commerce As Emerging Sector" - Rose Sheet, 31 Oct, 2016.)*

Colgate also said it does not feel pressure to launch an "aggressive" online sales strategy, even though it does have an e-commerce team and manages its online finances as a standalone business. *(Also see "P&G Keeps Direct-to-Consumer In Perspective, Retail Distribution Primary" - Pink Sheet, 26 Oct, 2016.)*

From the editors of The Tan Sheet.
Published online April 18, 2017

Claritin 'Be An Outsider' Campaign Links Bayer Brand And Public Health

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Bayer AG's US OTC drug business says its advertising aims in part to help improve consumers' health, and the latest digital media campaign for its *Claritin* antihistamine line says more time outdoors is one way most people can better their lives.

Advertising consultants give credit to **Bayer HealthCare LLC**'s "Be An Outsider" and other goodwill campaigns for keeping brands in consumers' attention, but some are not sold on the programs' effectiveness for generating sales.

"Be An Outsider" encourages people to get outside more, something that the 40% of US consumers with seasonal allergies could look to Claritin (loratadine or loratadine/pseudoephedrine) and other OTC allergy remedies and antihistamines to help them do. The campaign notes survey data show all US consumers on average spend 95% of their time indoors, the equivalent of 346 days in a year or 33 years in a span of 35 *(see box , p. 18)*.

"To us that was a startling signal that there is an inside epidemic in the United States," said Mike DiBiasi, vice president of allergy products for Bayer HealthCare, at a recent media briefing in New York city on the campaign and the survey.

"Claritin really has a role here to encourage people to be an outsider," he added.

DONATIONS PER PICTURE

Bayer is donating $5 to the Boys & Girls Clubs of America organization for every photo of people engaging in outdoor activity posted by June 30 on social media platforms using Be An Outsider or Claritin tags. Up to a total of $50,000 will be donated.

Be An Outsider images and videos will post to Facebook and Instagram and on the Claritin brand website, and retail store signs developed from those materials are a possibility in the second year of the campaign.

Non-Drowsy Claritin and other products in the antihistamine line are encouraging consumers to get outside more.

The firm also is launching a three-year commitment of $500,000 in funding for the organization, extending the support it provided during 2016 to refurbish Boys & Girls Club outdoor facilities in Atlanta and New York. The program this year supports development of an outdoor resource and activity guide to help support staff at 4,300 Boys & Girls Clubs to get local youth outside and during the next two years Bayer will work with the organization to determine key areas its funding can support, which may include refurbishing "outdoor play areas for select clubs in need," according to the firm.

Bayer launched the campaign on April 4 with an appearance in New York by actor Josh Duhamel, who engaged in outdoor activities with children from schools in the city and spoke with them about health benefits from being outside.

Like Bayer's current "HeroSmith" ad campaign to promote carrying aspirin for use as an immediate response to a heart at-

INDOOR TIME ADDS UP

In a Bayer-sponsored study to determine how much time US consumers are outside, Columbia University researcher Matthew Neidell,analyzed data from the federal Bureau of Labor Services' 2015 American Time Use Survey, which asked 40,000 people ages 15 and up about their daily activities and the amount of time used for each.

The average for respondents across the survey was 95% of their time inside, which includes commuting and other travel in addition to working indoors and sleeping, watching TV and other activities typically done in a person's home.

The most indoor time among consumers in large US cities was 97% in Baltimore, with Dallas and Miami at 96%, while Seattle consumers were inside the least, 93%, Neidell, an associate professor in health policy and management at Columbia's Mailman School of Public Health, determined from the data.

He said the data showed little variance by consumers' age, gender, location or other demographics. The largest chunk of time each day goes to sleeping, 37.1%, while watching TV is the next largest time block, 12.3% of a consumer's day on average.

The data analysis also showed among consumers' indoor time:

- 5% is used traveling;
- 4.75% goes to relaxing and leisure;
- 4.58% is for at eating and drinking;
- 2.88% is needed for grooming.

"It's a national pattern that we're seeing everywhere," Neidell said.

Because time indoors account for so much of an average consumer's day, a small change makes a big difference in the time outdoors for most. For instance, a 1% change would mean 20% more outside for the average person.

"That is a sizable change," said Neidell.

tack, Be An Outsider is on digital media only and is not planned to include TV commercials. HeroSmith launched in Fort Smith, Ark., earlier in 2017 and is planned for additional locations around the US in 2018. *(Also see "Bayer Plans 19 Consumer Product Launches To Revive Sluggish Sales" - Pink Sheet, 23 Feb, 2017.)*

And both campaigns aim to connect with consumers through goodwill from Bayer and its brands.

DiBiasi acknowledged that a firm the size of Bayer and a brand as established as Claritin could use numerous strategies, including reducing prices, to promote products and boost sales. Instead, Be An Outsider and HeroSmith show Bayer brands' interest in improving consumers' lives, he said.

"It's the power to good in the world that a brand can exhibit," DiBiasi said.

ALL BENEFIT, NO RISK?

DiBiasi also acknowledged that cynical responses or reviews are likely to Bayer's goodwill campaigns. "The easiest thing to do is to do nothing because you don't open yourself up to criticism. At Bayer, that's not what we're going to do."

What consumers will do in response to Be An Outsider, HeroSmith and similar campaigns linking a brand with a beneficial cause is difficult to gauge, advertising consultants say. Improved consumer opinion of a brand could result, but higher sales might not track with it.

"That's their hope but you're dealing with a smarter, much more brand-literate consumer segment," said Robert Passikoff, founder and president of Brand Keys Inc. in New York.

Millennial generation consumers make up much of the target audience for most advertising, particularly through social medial and other digital platforms, and they are "probably the most demanding consumer segment in marketing history," Passikoff said in an interview.

He noted that pharmaceutical firms, in general, probably have ample room for improving their images with consumers. "You want to try and leverage whatever you can in terms of good faith, corporate responsibility and so forth."

George Quesnelle, senior strategic advisor at consultancy Pinney Associates in Bethesda, Md., had experience with similar campaigns when he was with **GlaxoSmithKline PLC**. "We called it doing well while doing good," he said in an email.

Other current examples of consumer product brands promoting goodwill and their products are those supporting the Susan B. Cormen Foundation to help fight breast cancer, Quesnelle said.

"I actually think that tying a brand to a cause can be a very good thing for the brand and the cause. It generates contributions to the cause and creates goodwill for the brand," he said.

"In the past, brands I have had responsibility for developed relationships with the American Cancer Society and the Asthma and Allergy Society as well as participating in the Susan B. Cormen promotions. I see nothing but benefit coming out of it for the brand and the cause."

From the editors of The Tan Sheet. Published online April 18, 2017

State-Owned Pharma Group On Horizon As Korea Eyes Secure Supplies

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South Korean lawmakers are preparing a bill to create a state-owned pharma company in the country to meet a growing need to stabilize drug supplies and to promptly respond to potential public health crises such as the massive spread of infectious diseases, natural disasters, and terror attacks.

The need for a state-owned pharma firm in the country has been raised repeatedly in the past, but this is the first time that actual progress has been made on the idea. A number of other countries including Thailand, India, Indonesia and Brazil all already have state-run pharma firms that mainly manage the supply of essential drugs.

Shutterstock: one photo

PROPOSED STRUCTURE

According to an initial draft prepared by lawmakers of the proposed act to establish and manage a state-owned pharma firm, the public company would be established under the Ministry of Health and Welfare. It would produce and import "public medicines" and the health minister would conduct the research, statistical work, and investigations required for the management of such drugs.

Public medicines refers to vaccines and drugs to deal with public health crises or that are required for other treatment that pharma firms currently avoid producing or importing due to low profitability, orphan products used to diagnose or treat rare diseases, drugs used in foreign aid program, and other medicines that are essential in the treatment of diseases.

Lawmakers are reportedly set to finalize the bill and submit it to parliament next month for political debate.

NEED FOR STABLE SUPPLIES

The proposed establishment of a state-owned pharma group further beefs up the South Korean government's efforts to stabilize the supplies of critical medicines. Late last year, it unveiled plans to supply a range of essential drugs, drawing up a list of core products to monitor, stockpile and manage. *(Also see "Korea Lays Essential Drug Plans Amid Ongoing Supply Concerns" - Pink Sheet, 12 Dec, 2016.)*

During a recent public hearing in Seoul, lawmakers, government officials and experts also largely agreed on the need to set up such a "control tower" to guarantee public access to essential medicines.

"Through a state-owned pharma, we aim to deal with public health crisis situations such as the spread of infectious diseases, war, earthquake, leakage of radioactive substances, and terror attacks using viruses and germs. In normal times, the pharma company will aim to stabilize supply of essential drugs in areas that the market can't fulfill its roles," Mi-Hyuk Kwon of the main opposition Minjoo Party of Korea said in a statement prepared for the hearing.

Private sector experts who participated in the hearing also called for a stronger role for the government to manage and intervene in production and supply of drugs through ways such as parallel imports, compulsory licensing, and cooperation with the private sector.

CURRENT SHORTCOMINGS

At present, essential drugs are managed by the Health Insurance Review & Assessment Service, while orphan and other drugs subject to special reporting are handled by the Ministry of Food and Drug Safety, and vaccines and antiviral drugs relevant to public health are managed by the Centers for Disease Control & Prevention.

However, if these drugs are managed separately by different institutions, there is a risk of possible supply disruptions during public health emergencies.

"We largely depend on imports of vaccines and essential drugs at times of emergency, but supply has been unstable. The country has to integrate management of drugs so that safety of the nation isn't compromised," said Mi-Ae Choo, leader of the Minjoo Party of Korea.

During public health crises such as outbreaks of new types of influenza, MERS, and tuberculosis, vaccine and drug supplies should be stable, but under the current management system they have been

halted occasionally. The biggest reason has been low profitability for manufacturers.

Now, pharma companies can halt supplies if they report the reason for the suspension to the government within 10 days. The suspension can happen without the government's approval, and under the current system, when supply is halted, the government can't force the manufacturer to produce the drug or immediately supply an alternative.

In fact, there have been multiple instances of supply disruptions in South Korea:

- Kyowa Hakko Kirin Korea declared suspension of mitomycin supply after a price cut in 2012. The government had then requested the company to import the drug on worries this would hurt treatment of patients and the firm's headquarters accepted this;
- Supply shortage of *Tamiflu* (oseltamivir) in 2009 and 2010 as doctors widely prescribed the drug;
- Herpes zoster vaccine supply shortage in 2013 due to a sharp increase in demand;
- During an outbreak of influenza in 2009, it was difficult to launch a vaccine due to lack of legal grounds for prompt supply of the vaccine.

These experiences have created political pressure for the government to come up with measures to prevent drug access disruptions due to pharma firms' refusal to promptly supply drugs during public health crisis situations.

"It is time for the country to actively intervene to comprehensively manage import, production and supply of drugs. Establishment of a state-owned pharma may be one way to do this," declared Sang-Ho Woo, floor leader of Minjoo Party of Korea.

VACCINE ISSUES

The pandemic flu outbreak of 2009 also threw light on issues with vaccine supply. Major countries that produce vaccines could easily secure these, but South Korea had to make strong efforts, and the country also faced a similar situation when it had to procure Tamiflu.

In 2016, South Korea's self-sufficiency in vaccines was just 39%, while in Japan it was 59% and the US 100%. Many types of vaccines can't be produced and supplied domestically, so the country is highly dependent on imports.

Of South Korea's 12 required vaccinations, only six can be produced in the country, while aside from state-required vaccinations, of the 11 other vaccines available from private medical institutions, only two are produced domestically.

Given that unused vaccines have to be discarded after their expiration dates, such costs can work as a risk factor for producers, so South Korea needs to come up with measures to smoothly provide vaccines through increased R&D support, participants at the hearing on the state pharma group bill said.

From the editors of PharmAsia News. Published online April 15, 2017

Drug Prices: How US FDA Can Foster Competition Beyond Generic Approvals

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Shutterstock: Sherry Yates Young

The US FDA could have a hand in creating, not just approving, generic competition aimed at lowering the price of off-patent, monopolistic drugs, according to former agency Commissioner Andrew von Eschenbach, now president of Samaritan Health Initiatives.

During an April 19 drug pricing policy discussion hosted by the Atlantic magazine and underwritten by **Eli Lilly & Co.**, von Eschenbach discussed how FDA might help correct situations like the now-infamous pricing scheme engineered by Martin Shkreli and **Turing Pharmaceuticals AG** for *Daraprim* (pyrimethamine), which was off patent but had no competition.

Von Eschenbach began by stating it's not FDA's job to control pricing but the agency can help control drug costs by facilitating the drug development process. That is in line with, and expands upon, the often-discussed goal of faster generic approvals, a remedy for drug pricing also embraced by FDA commissioner-nominee Scott Gottlieb. *(Also see "Complex Generics: Gottlieb Eyes FDA Policy Changes To Speed Approvals" - Pink Sheet, 5 Apr, 2017.)*

"In my opinion, FDA should have zero, no role whatsoever, in de-

termining the price of a drug or any medical product," von Eschenbach said. However, "if one looks as drug development across its entire spectrum, there are a number of places along the road where the FDA can intervene with appropriate regulatory policy that can reduce costs."

The agency's efforts to bring additional vaccine producers online in 2006 during the avian flu epidemic as an example of how FDA can help nurture more competition in the market, he said. In that case, the issue was a lack of supply, not price. But von Eschenbach's point was that the agency proactively helped companies enter the market.

"When we were faced with bird flu, H5N1, we only had two licensed vaccine manufacturers in the country," he said. In order to create capacity, FDA took a very proactive stance of going out and engaging with companies and helping them to be able to meet good manufacturing practices … so they would be able to come back into the manufacturing of vaccines.

"It was not necessarily [FDA] going out and paying someone to create an alternative to the monopoly, but it was nurturing the ability for companies to come in and engage by helping them to adapt to the regulatory requirements that were going to be necessary," he explained. "FDA as a regulator can play an extremely important role in facilitating the ability for companies to participate in the marketplace and that translates into more competition and lower prices."

Von Eschenbach, who was FDA commissioner at the end of the George W. Bush administration, offered his example as a variation on an earlier suggestion by his co-panelist, Project HOPE Senior Fellow and Economist Gail Wilensky. She proposed that the federal government could step in to subsidize competition in narrow situations like that involving Daraprim.

Wilensky served in the George H.W. Bush Administration as head of what was then the Health Care Financing Administration and is now the Centers for Medicare and Medicaid Services.

"It's a problem that if the government wanted to be more proactive [in addressing], it could," Wilensky said. "If you get a small-use drug that is off patent and somebody increased the price in an extraordinary way, you could imagine a world in which the government actually pays a competitor to come in and be the second producer."

> "There isn't anyone in the federal government whose responsibility it is to worry about the prices for drugs." – Johns Hopkins' Anderson

However, she cautioned, this would only work "in a relatively limited case where you are not talking about breaking patents, because I think that's a very dangerous road to go down."

But "in the case where you have a generic that is a very small market that has been ignored by everyone except one producer, you could have the threat that the government will subsidize a second producer to come in on the generic side for these … spectacularly bad actors we've heard about in the last few years."

FORMAL GOVERNMENT OVERSIGHT OF DRUG PRICING

The panel discussion highlighted the current challenge of addressing drug pricing in the US – the fact that the issue is not really in the bailiwick of any federal agency, Johns Hopkins School of Public Health professor Gerard Anderson pointed out.

"Who's responsible for this whole issue of drug pricing?" he asked. "FDA has a small role and doesn't really want one. CMS has a role but has given a lot of it to" Medicare Part D drug plans. "There isn't anyone in the federal government whose responsibility it is to worry about the prices for drugs."

If "I was Donald Trump and I was asking, 'who's responsible in the federal government for drug pricing?' I don't know where I would turn, and I think that's a serious problem."

Published online April 20, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Discussion of six drug substances nominated for inclusion on the section 503A Bulk List eligible for compounding: nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide disodium reduced, nettle (Urtica dioica) whole plant, ubiquinol, vanadyl sulfate and artemisinin. Also, discussion of oral solid modified-release drug products that employ coated systems, nominated for the "Difficult to Compound" list.	Pharmacy Compounding	May 8
Recommendations on the agency's Innovation Funds work plan as prescribed in Sec.1002 of the 21st Century Cures Act	Science Board	May 9
NX Development Corp.'s 5-aminolevulinic acid hydrochloride powder (for oral solution) for use as an imaging agent to facilitate the real-time detection and visualization of malignant tissue during glioma surgery	Medical Imaging Drugs	May 10
Considerations for evaluation of respiratory syncytial virus vaccine candidates in seronegative infants	Vaccines and Related Biological Products	May 17
Puma Biotechnology's neratinib maleate for single-agent, extended adjuvant treatment of adults with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy	Oncologic Drugs	May 24
Emmaus Medical's L-glutamine powder (oral solution) for the treatment of sickle cell disease	Oncologic Drugs	May 24 (afternoon)
Hospira's (Pfizer) proposed biosimilar to Amgen Inc.'s *Epogen*/*Procrit* (epoetin alfa) for all of the indications on the reference biologic's labeling	Oncologic Drugs	May 25

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