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Pharma Pricing, Non-Profit Ties Get Increasing Scrutiny From Prosecutors

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Drug makers have been unable to shake free of government investigations of their marketing and sales practices. But the focus of the probes has shifted in the last few years and one word now routinely pops up – pricing.

That has been the hot button issue roiling industry the past year as several companies have been excoriated by Congress and the media for their steep price hikes. The Department of Justice has also honed in on the issue. It is investigating firms 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.

A look at recent Securities and Exchange Commission filings of more than a dozen pharma companies shows the practices that have drawn government attention. At least four companies – Biogen Inc., Celgene Corp., Gilead Sciences Inc. and Jazz Pharmaceuticals PLC – have received subpoenas for information about their relationships with charitable organizations. Mylan NV was subpoenaed for material about the pricing of its generic doxycycline and communications with competitors. And Valeant Pharmaceuticals International Inc. is facing several probes about its pricing and patient assistance programs (*see chart, p. 5*).

Mylan's doxycycline price increases were called out by Sen. Bernie Sanders, I-Vt., and Rep. Elijah Cummings, D-Md., in October 2014 when they sent letters to 14 generic drug makers about the pricing of their products. They noted that from October 2013 to April 2014, the average price charged for a 500-count bottle of 100 mg tablets had risen from $20 to $1,829, an 8,281% increase.

Mylan is now under fire for repeatedly raising the price of its severe allergy treatment *EpiPen* (epinephrine), which has increased from about $100 for a two-pack in 2008 to more than $600. Members of Congress sent a flurry of letters to the company requesting an explanation for the price hikes.

And on Sept. 6, New York Attorney General Eric Schneiderman announced that his office has begun an investigation into Mylan with regard to EpiPen, saying a preliminary review revealed that Mylan may have inserted potentially anticompetitive terms into its EpiPen sales contracts with numerous local school systems.

GOING BEYOND MISBRANDING CASES

The government has subpoenaed several other generic companies about their pricing. Most recently, Sun Pharmaceutical Industries Ltd. reported that it had received

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inside:

a subpoena for information pertaining to the pricing of its generic drugs.

In previous years, the DOJ has concentrated on claims of off-label marketing and payment of kickbacks. These investigations resulted in a slew of settlements, many topping $1bn.

Hogan Lovells partner Meredith Manning said she thinks the government is trying to avoid cases alleging misbranding under the federal Food, Drug, and Cosmetic Act and is looking for other theories of liability.

"They run into First Amendment issues when they go down the misbranding route, and juries don't want to convict individuals," Manning, a former attorney in FDA's Office of Chief Counsel and a former assistant US attorney, said.

Indeed, in the last six months the government has struck out in two trials against individuals and got a limited conviction in a third. In March, a Texas jury found Vascular Solutions Inc. and its CEO Howard Root not guilty of off-label marketing of its Vari-Lase vein ablation device. In June, a Boston jury cleared Carl Reichel, former president of Warner Chilcott PLC's pharmaceutical division, of conspiring to pay kickbacks to physicians.

And in July, another Boston jury acquitted former executives of Johnson & Johnson's Acclarent Inc. division of felony charges while convicting them on misdemeanor counts in a case involving marketing a sinus dilation device for use with a steroid.

WILL INDIVIDUALS BE PROSECUTED?

King & Spalding partners John Richter and Michael Pauzé, who represented Vascular Solutions in the government›s case, said they expect the DOJ to continue to prioritize the investigation and prosecution of individuals. They noted that there has been increasing pressure on the department to go after individuals, which culminated in a September 2015 memo from Deputy Attorney General Sally Quillian Yates to assistant attorneys general and all US attorneys outlining steps to overcome challenges to pursuing individuals in corporate misconduct.

However, Richter, a former US Attorney and former Acting Assistant Attorney General in charge of the criminal division at DOJ, said that there is a big difference between issuing policy and standing in front of a judge and trying to prove culpability. As a prosecutor, there is a «big distance between what you wish in the case and what can be proven in the case,» he said. "If you get enough bad outcomes it will make you gun shy."

As for the focus of government investigations, both emphasized that the growth in federal regulation has meant and will continue to mean growth in federal enforcement. Pauzé, a former assistant US attorney, said that because there is so much talk about pricing it can lead to government scrutiny. Richter added that despite the significant setbacks the government has faced in off-label cases recently that area of inquiry is not dead.

GOVERNMENT CLOSES NOVARTIS, TEVA INQUIRIES

Many government investigations evolve from False Claims Act complaints in which private individuals, known as relators, file suit on behalf of the federal government alleging fraudulent claims have been submitted for government payments. If the government intervenes in the case the relator receives up to 30 percent of the recovery.

Richter said there has been a tremendous increase in plaintiff law firms representing alleged whistleblowers, which has led to an uptick in FCA cases being brought to the Justice Department for consideration.

However, the government frequently declines to intervene in these complaints. For example, Novartis AG reported that in the third quarter of 2015, the US Attorney's Office for the Western District of Kentucky declined to intervene in a relator's complaint and closed an investigation it had initiated in 2012 relating to marketing practices for several Novartis products.

The US Attorney for the Southern District of New York declined to intervene in a False Claims Act case against Teva Pharmaceutical Industries Ltd. It had issued a civil investigation demand to the company in 2014 for documents related to the sales and marketing of *Copaxone* (glatiramer) and *Azilect* (rasagiline). The government also declined to intervene in two complaints alleging Cephalon (now Teva) promoted the sleep disorder drugs *Nuvigil* (armodafinil) and *Provigil* (modafinil) off-label. The whistleblowers in these cases are pursuing the actions on their own.

Several other investigations have resulted in DOJ settlements. Among the most recent, Pfizer Inc. agreed to pay $784.6m to resolve allegations that its Wyeth subsidiary paid hospitals steep discounts if they purchased both oral and IV formulations of the acid-suppressant *Protonix* (pantoprazole). And Roche and OSI Pharmaceuticals LLC reached a $67m settlement to resolve claims they misrepresented the effectiveness of the non-small cell lung cancer drug *Tarceva* (erlotinib) (*see story p. 6 for list of settlements*).

In addition to US healthcare fraud queries, the government is also stepping up investigations of foreign bribery. This year the DOJ increased the number of prosecutors looking into potential violations under the Foreign Corrupt Practices Act and initiated a pilot program to give companies credit and a reduction in fines for their cooperation. At least six companies are the subject of ongoing FCPA-related investigations.

Earlier this year, Novartis and SciClone Pharmaceuticals Inc. reached settlements of $25m and $12.8m, respectively, for payments made to healthcare professionals employed at state health institutions in China to induce them to prescribe their products. And on Aug. 30, the SEC announced that AstraZeneca PLC agreed to pay $5.5m to settle charges that its subsidiaries in China and Russia made improper payments to foreign government employees.

STATE OPIOID ACTIONS

In addition to federal government probes, pharma companies also face investigations and lawsuits from states. Most notably, several states and counties have sued opioid manufacturers alleging deceptive marketing of their pain products.

The City of Chicago filed a lawsuit against Purdue Pharma LP, Teva, Johnson & Johnson, Endo Pharmaceuticals Inc. and Actavis in June 2014 alleging they marketed their opioids to encourage people to use them beyond their approved indications. A district court judge dismissed the suit and terminated Teva as a party. However, the judge allowed Chicago to amend its claims

and the city filed a second amended complaint in November.

California's Santa Clara County and Orange County filed a similar complaint against opioid manufacturers in 2014. Last year, the court stayed the case until FDA concludes its ongoing inquiry into the safety and effectiveness of long-term opioid treatment. In December 2015, the state of Mississippi filed a complaint against most of the same group of companies. And on Aug. 31, New York's Suffolk County filed a similar suit in New York Supreme Court against Purdue, Teva, J&J and Endo.

Other states are also pursuing actions against opioid makers. In August 2015, the New Hampshire Attorney General subpoenaed Janssen and other pharma companies related to their opioid marketing practices. J&J has challenged the subpoena.

A few companies have settled opioid state probes. In December, Purdue reached a $24m settlement with Kentucky's Attorney General to resolve allegations it misrepresented the addictive nature of *OxyContin* (oxycodone) and encouraged doctors who were not trained in pain management to overprescribe it. In March, Endo agreed to establish an opioid abuse and detection program in a settlement resolving the New York Attorney General's investigation of *Opana ER* (oxymorphone extended release) marketing. And in July, Pfizer inked an agreement with the City of Chicago that helped it avoid being a party to the city's litigation against other manufacturers.

As for the future of government investigations, attorneys expect to see them continue to increase.

"Healthcare is such an important issue in this country politically and will be for the foreseeable future," King & Spalding's Pauzé said. "It will continue to be a focus of criminal investigations and prosecutions."

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Pharma Companies Under Government Investigation

COMPANY	INVESTIGATION
AbbVie	Alaska Attorney General's Office served a civil investigative demand, primarily seeking documents AbbVie produced in the Federal Trade Commission's suit against AndroGel patent litigation settlement; suit was dismissed in May 2015.
Allergan	In April 2015 Allergan's Forest subsidiary received a subpoena from HHS' Office of Inspector General requesting documents relating to average manufacturer and best price calculations for several of its products. In June 2015 the company's Actavis subsidiary received a subpoena from DOJ seeking information relating to the marketing and pricing of certain generic products and its communications with competitors about the products (Teva assumed liability with its acquisition of Allergan's generic business). Allergan has received investigatory subpoenas from the US Attorney's Office and various state agencies requesting information and documents relating to categories of drug pricing, including average wholesale price, wholesale acquisition cost, average manufacturer price and best price.
AstraZeneca	In May 2012 its MedImmune unit received a subpoena form the Office of Attorney General for the State of Florida Medicaid and Fraud Control Unit requesting sales and marketing documents for its respiratory tract disease treatment *Synagis* (palivizumab). In June 2011 MedImmune received a demand from the US Attorney's Office for the Southern District of NY requesting documents related to Synagis and also received a court order to produce the documents for the Office of the Attorney General for the State of New York Medicaid and Fraud Control Unit.
Biogen	In March 2016 received a subpoena from the federal government for documents relating to the company's relationship with non-profit organizations that provide assistance to patients taking Biogen drugs. In July received civil investigative demands from the federal government for documents and information relating to treatment of certain service agreements with wholesalers when calculating and reporting average manufacturing prices in connection with the Medicaid drug rebate program.
Celgene	In December 2015 received a subpoena from the US Attorney's Office for the District of Massachusetts requesting documents related to its support of 501(c)(3) organizations that provide financial assistance to patients.
Eli Lilly	US Attorney's Office for the Eastern District of Pennsylvania and the DOJ are conducting an inquiry of Lilly's treatment of certain distribution service agreements with wholesalers when calculating and reporting average manufacturer prices in connection with the Medicaid drug rebate program. Lilly was notified of the probe in September 2015.
Gilead	In February 2016 received a subpoena from the US Attorney's Office for the District of Massachusetts requesting documents related to its support of 501(c)(3) organizations that provide financial assistance to patients and its provision of financial assistance to patients for hepatitis C virus products. Massachusetts Attorney General served Gilead with a civil investigative demand in February requesting documents related to its HCV products and in July suspended Gilead's obligations under the CID until further notice.

COMPANY	INVESTIGATION
GlaxoSmithKline	In February 2016 the US Attorney's Office for the Southern District of New York issued a subpoena requesting documents related to GSK's vaccine business and in March 2016 it issued a subpoena requesting documents relating to US contracts for its migraine treatments Imitrex (sumatriptan) and Amerge (naratriptan).
Jazz Pharmaceutical	In May 2016 received a subpoena from the US Attorney's Office for the District of Massachusetts requesting documents related to the company's support of 501(c)(3) organizations that provide financial assistance to Medicare patients and for documents regarding financial assistance to Medicare patients for its narcolepsy drug *Xyrem* (sodium oxybate).
Johnson & Johnson	In March 2016 its Janssen Pharmaceuticals unit received a civil investigative demand from the US Attorney's Office for the Southern District of New York related to Janssen's contractual relationships with pharmacy benefit managers from Jan. 1, 2006 to the present with regard to certain products. In August 2015 the New Hampshire Attorney General subpoenaed Janssen and other pharma companies related to opioid marketing practices. In March 2016 New Hampshire Superior Court denied the state's motion to enforce the subpoena and granted a protective order on grounds the state had not obtained approvals to retain private counsel. The parties appealed the ruling and the AG's office obtained approvals for private counsel.
Mylan	In December 2015 received a subpoena from DOJ's antitrust division seeking information relating to the marketing, pricing and sale of its generic doxycycline products and any communications with competitors about them. The company also received a subpoena from the Connecticut Office of the Attorney General seeking information about doxycycline and its other generic products. And in September the New York Attorney General's Office began an investigation of its EpiPen sales contracts.
Novartis Pharmaceuticals	In 2013 the government filed a civil complaint intervening in a False Claims Act action involving marketing practices for several cardiovascular medicines. The probe is related to a 2011 investigation by the US Attorney's Office for the Southern District of New York. In 2013 received a civil investigative demand from the US Attorney's Office for the Southern District of New York requesting documents and information related to marketing practices for its multiple sclerosis drug *Gilenya* (fingolimod), including the remuneration of healthcare providers.
Sanofi	In June 2012 DOJ began investigating disclosures to the FDA regarding the variability of response to the blood thinner *Plavix* (clopidogrel).
Valeant	In March 2016 received an investigative demand from the North Carolina Department of Justice for materials relating to Nitropress (nitroprusside), Isuprel (isoproterenol) and Cuprimine (penicillamine), including documents regarding production, marketing, distribution, sales and pricing, and patient assistance programs. In October 2015 received subpoenas from the US Attorney's offices for the District of Massachusetts and the Southern District of New York for documents relating to patient assistant programs; its former relationship with Philidor and other pharmacies; accounting treatment for sales by specialty pharmacies; information provided to the Centers for Medicare and Medicaid Services; pricing, including discounts and rebates, marketing and distribution of its products; its compliance program; and employee compensation. In September 2015 received a letter from DOJ's civil division and the US Attorney's Office for the Eastern District of Pennsylvania regarding investigation of Biovail Pharmaceutical's treatment of certain service agreements with wholesalers when calculating and reporting average manufacturer prices in connection with the Medicaid drug rebate program.

Source: Company SEC filings

Pharma Deals With The DOJ

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Four years ago, pharmaceutical companies were forking out huge payments to the US Department of Justice to resolve allegations of improper marketing of their products.

GlaxoSmithKline PLC set a new record in July 2012 with its $3bn. settlement to resolve three separate government investigations. It was the fourth company to reach a deal in excess of $1bn. The first to do so was Eli Lilly & Co., which in 2009 paid $1.4bn for marketing its atypical antipsychotic *Zyprexa* (olanzapine) for unapproved uses. That deal was surpassed a few months later when Pfizer Inc. entered a $2.3bn settlement for off-label promotion of four drugs and kickbacks involving nine other products. And Abbott Laboratories Inc. joined the billion dollar club in May 2012 when it agreed to pay $1.5bn and pled guilty to promoting its neuro-

logic drug *Depakote* (divalproex) off-label.

Since then the size of settlements has dropped. Only one company has reached an agreement of that magnitude, Johnson & Johnson with its $2.2bn settlement resolving criminal charges of off-label promotion and kickbacks involving its atypical antipsychotic *Risperdal* and two other drugs (*see chart below of agreements reached in the last three years*).

The government was then going after companies primarily for marketing drugs for unapproved uses and making payments to health care providers to induce them to prescribe their products. More recently, the DOJ has begun to look at other practices, particularly those related to drug pricing.

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Drug Maker Settlements With Department of Justice

YEAR	COMPANY	SETTLEMENT
June 2016	Roche and OSI Pharmaceuticals	Companies agreed to pay $67m to resolve claims they misrepresented the effectiveness of the non-small cell lung cancer drug Tarceva (erlotinib), diverting patients from first-line treatments.
March 2016	Johnson & Johnson	J&J's Acclarent subsidiary reached an $18m settlement to resolve allegations of off-label promotion of its Relieva Stratus MicroFlow Spacer product as a drug delivery device. On July 2016, the former CEO and former VP of sales were convicted of misdemeanor violations.
February 2016	Pfizer	After a seven-year legal battle, Pfizer agreed to pay a $784.6m fine to resolve complaint its 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.
October 2015	Novartis	Reached a $390m settlement with DOJ and several states to resolve a civil complaint alleging it paid kickbacks to specialty pharmacies to induce them to recommend that patients order Novartis drugs Myfortic (mycophenolic), Exjade (deferasirox), Tasigna (nilotinib), Gleevec (imatinib) and TOBI (tobramycin).
October 2015	Warner Chilcott	Pled guilty to illegal promotion of several drugs and agreed to pay $125m to resolve criminal and civil liability alleging kickbacks and improper sales and marketing.
February 2015	AstraZeneca	Reached a $7.9m settlement to resolve allegations it paid kickbacks to Medco Health Solutions for preferred formulary placement of its heartburn drug Nexium (esomeprazole).
January 2015	Daiichi Sankyo	Agreed to pay federal government and state Medicaid programs $39m agreement to resolve allegations it paid kickbacks to induce physicians to prescribe its cardiovascular products.
September 2014	Shire Pharmaceuticals	Agreed to pay $56.5m to resolve civil allegations of improper marketing of several drugs, including that it promoted its attention deficit hyperactivity disorder drug Adderall XR for certain uses without supporting clinical data and overstated the drug's efficacy.
April 2014	Astellas Pharma US	Agreed to pay $7.3m to resolve allegations it marketed the antifungal Mycamine off-label for pediatric use.
March 2014	AstraZeneca	Agreed to pay $27.6m to DOJ and state of Illinois to resolve allegations of kickbacks to one doctor.
February 2014	Endo Health Solutions and Endo Pharmaceuticals Inc.	Agreed to pay $192.7m to resolve criminal and civil liability from marketing Lidoderm (lidocaine patch) for unapproved uses; Endo admitted the claims in a deferred prosecution agreement.
November 2013	Johnson & Johnson	As part of $2.2bn settlement pled guilty to marketing atypical antipsychotic Risperdal for off-label uses to elderly patients and resolved civil allegations of marketing newer antipsychotic Invega (paliperidone) and congestive heart failure drug Natrecor (nesiritide) for unapproved uses and paying kickbacks to physicians and Omnicare.
July 2013	Pfizer	Wyeth subsidiary pled guilty to off-label marketing of the immunosuppressive drug Rapamune (sirolimus) and agreed to pay $490.9m to resolve criminal and civil liability.
May 2013	Ranbaxy	Ranbaxy USA Inc. subsidiary pled guilty to seven felony counts and agreed to pay $500m to settle criminal and civil allegations involving data fraud and drug manufacturing violations.

Biosimilar Launch Notification May Head Back To Court

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Apotex Inc. has followed Sandoz in urging the Supreme Court to review an appeals court ruling that delays the launch of a biosimilar until six months after FDA licensure.

Apotex filed a petition on Sept. 9 challenging the US Court of Appeals for the Federal Circuit's decision that a biosimilar sponsor is required to provide the innovator company 180-day notice of commercial marketing *after* FDA approval whether or not it engages in the patent information exchange process laid out in the biosimilar statute.

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The July ruling was the second time the Federal Circuit had addressed the issue. In July 2015 a divided panel had found that the Biologics Price Competition and Innovation Act (BPCIA) requires notice after approval. That case involved Sandoz Inc.'s early notice of commercial marketing of *Zarxio* (filgrastim-sndz), a biosimilar to Amgen Inc.'s *Neupogen* (filgrastim).

Apotex had argued that the Sandoz ruling did not apply in its case since unlike Sandoz it had provided Amgen with its application and manufacturing process for a biosimilar to *Neulasta* (pegfilgrastim). But a unanimous panel said Apotex was making "a factual distinction, not a legally material distinction" between its situation and Sandoz's. The panel said the final biosimilar product cannot be known with certainty until FDA licenses it.

The court also said it expected the six-month launch delay to occur less frequently over time as more reference products will be newer and biosimilar applicants will be able to file an application four years after licensure of the reference product. It suggested that FDA could license a product six months before expiration of the innovator's 12 year period of exclusivity.

TENTATIVE APPROVALS MAY NOT BE POSSIBLE

"We believe this is a misconception," Steve Lydeamore, president of Apotex's biosimilars unit Apobiologix, said of the idea that the 180-day launch notification will not impact newer products. He noted that there is no provision in the BPCIA for the FDA to grant tentative approval.

"Even if the brand is protected by 12-year exclusivity, there is no reason to believe it won't be extended six months," Lydeamore said. "This will hit every biosimilar, even when one is already on the market."

Apotex's petition says the Federal Circuit "has contorted the patent resolution procedures established by the BPCIA."

"The Circuit-manufactured 180-day extension of the period of exclusivity conferred by Congress to brand-name manufacturers has anticompetitive effects, prolongs the collection of monopoly rents, and bolsters already-troublesome barriers to entry for biosimilars," the petition states.

WAITING FOR THE SOLICITOR GENERAL

Sandoz, a unit of Novartis AG, filed a similar petition with the Supreme Court in February. It argued that nothing in the BPCIA text provides that an applicant must wait until FDA approves a biosimilar and then provide notice of its self-evident intent to market that approved biosimilar, and then wait six months before launching.

In June, the court asked the Solicitor General to provide the government's views on both the biosimilar launch notification and the patent information exchange provisions of the biosimilar statute. Amgen filed a brief opposing Sandoz's petition along with a conditional cross-petition asking the court to review the patent dance provisions if it granted Sandoz's petition.

The Solicitor General has yet to submit a brief. Now that the Federal Circuit has issued two decisions on the issue the Supreme Court may be more inclined to review the matter.

COURT CLEARS PATH, BUT BIOSIMILARS STILL IN FDA LIMBO

With its petition, Apotex is moving to eliminate any barriers to a launch once FDA approves both its pegfligrastim biosimilar, *Lapelga*, and its filgrastim biosimilar, *Grastofil*. On Sept. 6, the company won a court ruling that the two biosimilars do not infringe Amgen's manufacturing process patent. That patent was issued by the Patent and Trademark Office in February 2015 and expires on July 29, 2031. Amgen's composition patent expired in October 2015.

The big question is when the biosimilars will clear FDA. Apotex submitted its pegfilgrastim biologics license application in October 2014 and its filgrastim application in December 2014. The company has not disclosed any FDA action on the applications but FDA's latest Biosimilar User Fee Act Report suggests the agency issued a "complete response letter" for its pegfilgrastim within the 10-month review period. The agency is also likely to have issued a letter for filgrastim since the user fee action data has long passed.

Lydeamore declined to answer questions as to whether FDA has issued complete response letters and whether the agency has requested additional data. "We don't comment on applications while they are still under active review at FDA," he said.

Apotex established the Apobiologix division, originally called Global Specialty Pharma, last year. It is responsible for the development, manufacturing and commercialization of biosimilars and other specialty products.

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Biosimilar Interchangeability May Be Losing Luster As Approval Goal

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Interchangeability may be losing its luster as a goal for biosimilar development. Increasing concern and debate about drug costs seems to have made the FDA designation less desirable or less necessary to gain a foothold in the market.

Craig Wheeler, president and CEO of Momenta Pharmaceuticals Inc., said during the Generic Pharmaceutical Association's recent Biosimilars Council Conference that the importance of interchangeability is not as high as prior years.

"At least for me, it is not as strong as it certainly first was when we entered this business," he said. "The cost pressures on health care might mean that regardless of interchangeability your program is going to be accepted."

Wheeler also said interchangeability cannot make up for late market entry.

"I think if you come late just being interchangeable isn't going to help you much at all," he said.

Interchangeability is considered a tougher standard to reach than biosimilarity and expected to require additional trials and a separate application. An interchangeable product would be expected to behave the same in patients if they are switched multiple times between it and the reference product.

That standard was thought to be one of the keys for growth of the biosimilar market in the US because it would allow for substitution at the pharmacy level.

In fact, among the fronts where innovator companies are battling biosimilar advocates is over state substitution laws that would require physician notification before substituting a biosimilar for a reference product.

SANDOZ STILL FEELS INTERCHANGEABILITY 'AN ABSOLUTE KEY'

FDA has approved three biosimilars, but has yet to name any of them interchangeable. Sandoz Inc., which has two approved biosimilars, *Zarxio* (filgrastim-sndz) and *Erelzi* (etanercept-szzs), already has said it eventually will pursue interchangeability for both products.

Zarxio, a biosimilar of Amgen Inc.'s *Neupogen* (filgrastim), was the first biosimilar FDA approved. Erelzi, a biosimilar of Amgen's *Enbrel* (etanercept), was approved in August.

Peter Goldschmidt, president of Sandoz US, said the issue is not black and white and that interchangeability will remain important for patients.

"I would say interchangeability is important because it creates less confusion," he said. "In the end, I would say you always look at it from the patient perspective and that's why I think interchangeability from our side has been an absolute key for our uptake of our biosimilars."

FDA has yet to release guidance on interchangeability. It remains one of industry's most anticipated biosimilar documents.

ECONOMICS OVER INTERCHANGEABILITY

It appears the ramped up debate on drug pricing has affected the perceived value of interchangeability.

Like small molecule generics, government and other stakeholders expect biosimilars to relieve pressure on consumers and stop the dramatic price hikes that have gained attention recently.

Ronny Gal, senior analyst at Sanford Bernstein and Co., said interchangeability is "not that important."

"I think biosimilar adoption is economics," he said.

Much of the uproar about pricing so far has focused on generics, rather than biologics.

The most recent example is that of Mylan NV's *EpiPen* (epinephrine), which continues to face a backlash from Congress and others over a dramatic price increase.

Stakeholders were hoping a generic version of the product would bring some competition and push the price down, but copying the injection device has proven a challenge.

TALKING THE PHYSICIAN OUT OF IT

Gal argued that even with interchangeable biosimilars, sponsors will not be able to avoid the patient talking to their physician about a substitution, suggesting that the process likely will not resemble the one in place for generics.

"The biosimilar is always going to come to the patient with a different box, which has a different color," he said. "It's going to have a different name on the box, which means that you have to call the patient ahead of time and tell them that you're putting them on a biosimilar product as opposed to the innovator product."

Gal continued: "You're not going to be able to get around this issue of talking to the physician or talking to the patient. So if you are leading the biosimilar race for a particular product, is interchangeability good for you or bad for you? I'm not so sure."

Indeed, presentation differences already have been identified as a potential problem with uptake of some of the first approved biosimilars.

Zarxio and Erelzi were approved with notations in their labels that dosing among some groups may not be ideal or possible.

Erelzi is not available in a lyophilized powder formulation like Enbrel, which FDA said in the label means that weight-based dosing for children less than 63 kg was not available.

Zarxio's syringe design also led to concerns about patients' and caregivers' abilities to administer partial doses. FDA advised against dosing below a certain level in the label.

Gal also asked whether biosimilar competition against interchangeable products will push prices down faster.

Wheeler said a FDA approval likely will cause payers to negotiate the best price possible.

"If the FDA deemed the product safe and effective, I think you're going to find they negotiate dispositive to the lowest cost you can possibly get," he said.

For payers and patients, that would be the ideal scenario. But it also is an area where innovator companies appear to be fighting hard to ensure that doesn't occur.

In a private meeting with FDA, AbbVie Inc., which is facing biosimilar competition from Amgen for its *Humira* (adalimumab), raised concerns about whether payers and providers may overestimate the value of switching data submitted as part of the 351(k) application.

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EU Pay-For-Delay Ruling Against Lundbeck Sends Signal To Others, Including UK Competition Body

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Last week's decision by the EU's General Court that the European Commission was right in 2013 to conclude that Lundbeck Inc. breached competition rules by signing pay-for-delay agreements with four generics companies sends a strong message to companies involved in or contemplating similar deals.

In the first ever EU ruling on the question of pay-for-delay agreements, the General Court on Sept. 8, 2016 upheld the commission's June 2013 decision to fine Lundbeck and four generics companies for agreeing to delay the marketing of generic versions of the Danish firm's antidepressant Celexa (citalopram).

It confirmed the commission's conclusion that the generics firms were potential competitors to Lundbeck when the agreements were reached, because without these deals they would have had "real concrete possibilities" of marketing their versions of citalopram. It said that Lundbeck had not been able to show that the restrictions set out in the agreements in question were objectively necessary to protect its intellectual property rights.

The commission welcomed the ruling, saying it showed it had been correct to find that the generics firms agreed with Lundbeck to stay out of the market in return for value transfers and other inducements, which according to the General Court constituted "a buying-off of competition." By paying the generics competitors "for their promise to stay out of the citalopram market," Lundbeck was "certain to avoid competition from the four companies for the entire duration of the agreements."

But Lundbeck said it "strongly" disagreed with the court's decision, claiming that the agreements did not restrict competition and "did not go beyond the protection already offered by society via Lundbeck's patent rights." It said it would study the judgment before deciding whether to appeal to the Court of Justice of the European Union.

As well as the parties concerned, the ruling will be of particular interest to the UK Competition and Markets Authority, which in February this year fined GlaxoSmithKline PLC for alleged market abuse in striking deals to delay the launch of generic versions of its antidepressant *Seroxat* (paroxetine). This case has now gone to appeal, and lawyers suggest the Lundbeck ruling could well bolster the CMA's position.

More broadly, though, there are also suggestions that the court has not given the commission a totally free hand in addressing future pay-for-delay cases, as it will have to carefully consider aspects of agreements between originator and generics companies such as the value and breadth of any settlements, and which forms of payment can be characterized as illegal.

THE AGREEMENTS

The Lundbeck case dates back to 2002 when the company entered into deals with a group of generics firms under which it paid tens of millions of Euros and other inducements for the latter to delay the marketing of their generic versions. The firms were Generics (UK) Ltd (then owned by Merck KGAA), Alpharma (whose human generics business is now part of Actavis), Arrow and Ranbaxy Laboratories Ltd.

At the time, Lundbeck's basic substance patent for citalopram had expired, but it held some related process patents that the commission said provided "more limited protection." Noting that the generics producers were preparing for market entry with much cheaper generic versions of citalopram, the commission said the agreements "gave Lundbeck the certainty that the generics producers would stay out of the market for the duration of the agreements without giving the generic producers any guarantee of market entry thereafter." It fined Lundbeck €93.8m ($105m) and the generics firms a total of €52.2m. The companies appealed the decision to the General Court.

In its Sept. 8 ruling, the court said that it considered, like the commission, that Lundbeck and the generic undertakings concerned were indeed potential competitors at the time the agreements at issue were concluded. It pointed out that in order to establish that an agreement restricts potential competition, it must be shown that, if the agreement had not been concluded, the competitors would have had "real concrete possibilities of entering that market."

It said it believed the commission had carefully examined the actual possibilities

the generics firms had of entering the market, relying on objective evidence such as the investments already made, the steps taken to obtain a marketing authorization, and the supply contracts concluded with suppliers of active pharmaceutical ingredients. It also noted that the generics firms had a number of possible routes to market, including an "at-risk" launch (i.e., facing the possibility of legal action from Lundbeck).

The commission, the court said, was entitled to conclude that the agreements at issue constituted a restriction of competition "by object" (i.e., they could be regarded as damaging to competition by their very nature, rather than in terms of the effects they had in practice).

"In that respect, the Court takes the view that Lundbeck did not demonstrate that the restrictions set out in the agreements at issue were objectively necessary in order to protect its intellectual property rights and, in particular, its crystallisation patent. Lundbeck could have protected those rights by bringing actions before the competent national courts in the event that its patents were infringed," the court declared.

What mattered, it said, was that the generic undertakings had "real concrete possibilities of entering the market at the time the agreements at issue were concluded with Lundbeck, with the result that they were exerting competitive pressure on the latter. That competitive pressure was eliminated for the term of the agreements at issue, which constitutes, by itself, a restriction of competition by object."

> "Patent settlement deals are efficiency enhancing and legitimate when there are bona fide grounds for dispute"

But in a statement issued after the ruling, Lundbeck said that more than 600 "meticulous analyses" of generic citalopram samples had shown that the generic was produced with infringing processes. "Furthermore, in many concurrent documents the generic companies acknowledged that their products violated Lundbeck's patents. Patent settlement agreements are efficiency enhancing and legitimate when there are bona fide grounds for dispute."

The company claimed it acted "transparently and in good faith" in trying to protect its patents. In 2004, it said, "the agreements were reviewed by both the European Commission and the Danish Competition Authority, who publicly stated that it was doubtful whether the agreements restricted competition and that the Commission therefore did not wish to initiate proceedings against Lundbeck."

RULING CAUSES UNCERTAINTY, SAYS EFPIA

Its dissatisfaction was shared by the European R&D industry body EFPIA, which said the ruling "disputes that patents are a legal bar to market entry that prevent potential competition within the scope of their claims. That creates uncertainty for many collaborative relationships between innovators with large patent portfolios."

EFPIA said it was "inappropriate" to classify a lawful settlement agreement as an illegal market-sharing cartel because early generic market entry constitutes potential competition, and that the complexity of patent litigation in the pharmaceutical sector "makes a presumption of unlawfulness without concrete analysis inappropriate."

Moreover, it continued, value transfers "must be considered against background of the considerable damage that the early entry of a generic – prior to patent expiry – may have in a market in terms of irreversible reimbursement price cuts and the knock-on effects caused by international reference pricing." It said the "fact or size of any value transfer must be considered in terms of the considerable and disproportionate economic risks at stake in Europe."

Merck KGaA told the Pink Sheet that it was considering an appeal against the ruling to the CJEU. It noted that the ruling concerned patent settlement agreements entered into between its former subsidiary Generics (UK) Ltd and Lundbeck, and that Merck had divested its entire generics business (to Mylan Laboratories Inc) in 2007.

Law firm Bristows observed that the judgment would be "of immediate interest for the parties involved in the paroxetine litigation" in the UK, particularly the CMA and the companies concerned.

In February 2016, the CMA fined GlaxoSmithKline and a number of generics firms including Generics UK (and its former parent Merck KGaA) and Actavis UK Ltd (formerly Alpharma Ltd) for entering pay-for-delay agreements on generic paroxetine. The CMA said these agreements "deferred the competition that the threat of independent generic entry could offer, and potentially deprived the National Health Service of the significant price falls that generally result from generic competition."

Bristows said that the CMA was likely to have aligned itself closely with the commission's 2013 decision on Lundbeck, and noted that an appeal of the CMA's decision is due to be heard by the UK Competition Appeal Tribunal early in 2017.

The court's ruling is "likely to be welcome news to the CMA," Bristows said. "Meanwhile, companies entering into agreements settling patent litigation will need to continue to pay very careful heed to the competition rules when deciding on the terms of market access for generic products," it commented.

Law firm Baker & McKenzie said that while the General Court had upheld the commission's decision and fines in full, "a close reading indicates that the Court has not handed the Commission a precedent that gives it an entirely free hand in pay-for-delay cases."

It said that the value of any payments (relative to profits), the breadth of the settlement, and whether it offers a free entry route to generics would "all be carefully weighed," and that the burden to prove illegality of settlements has been set "relatively high." The commission, it said, "must be able to prove that the generic would have launched at risk but for the settlement agreement."

Baker & McKenzie added that the court was also clear that not all payments can be characterized as illegal. "Where the payment is linked to the generic's anticipated profits, then this is evidence of a likely 'by object' illegal market exclusion agreement."

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Pediatric Rare Disease Voucher Program Faces Expiration

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Supporters of the 21st Century Cures bill want to use the expiring rare pediatric disease priority review voucher (PRV) as a way to push the legislation up Congress' priority list this month, but it is appearing increasingly unlikely, however, which could force advocates to find another vehicle to ensure the program continues.

The PRV program, which allows voucher holders to gain a transferable priority review for any application they choose, will expire on Oct. 1 without congressional action. Rare disease advocates are pushing patients and others to write their lawmakers to ensure the program is renewed without a lag.

One lobbyist suggested that the intent is to use the program to help make the House Cures package more attractive during the brief window for legislating before Congress departs once again for the final month of campaigning and elections.

Renewing the voucher program likely is not enough to push the Cures bill along, but it can help remove opposition and garner it more attention, the lobbyist said.

Indeed, National Organization for Rare Disorders Associate Director of Public Policy Paul Melmeyer told the Pink Sheet that the group's first choice is to renew the program through the 21st Century Cures bill.

Melmeyer didn't characterize the voucher program as leverage to help Cures.

"We are not necessarily looking to use anything as 'leverage,' but instead we're advocating for both the Cures package to pass and the PRV reauthorization to be included," he said in an email.

It is a gamble, however, given the other pressing issues already on Congress' agenda.

STAND-ALONE FALLBACK

If Cures cannot be done this month, which is a distinct possibility, NORD will push for passage of a standalone bill renewing the voucher program that is pending in the Senate called the Advancing Hope Act. The appropriations process also is a possibility for the renewal, Melmeyer said.

The program was extended until the Oct. 1 end of fiscal year 2016 in the 2015 omnibus appropriations bill. It had been set to expire in March 2016 in conjunction with a provision mandating the agency stop awarding vouchers a year after the third voucher was issued.

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> If Cures cannot be done this month, NORD will push for passage of a stand-alone bill renewing the voucher program pending in the Senate called the Advancing Hope Act.

Should the CR route fail, Congress also could pass a bill extending the program retroactively when it returns for a lame-duck session after the election, the lobbyist said.

A continuing resolution to keep the government running after Sept. 30 appears to be job number one.

There also are increasing calls for Congress to approve additional funding to fight the spread of Zika virus in the US. Senators tried, but could not pass a Zika bill Sept. 6. Both parties have been arguing over funding levels and other issues, which has delayed the bill.

That leaves the Cures bill, a wide-ranging package intent on helping innovative treatments reach patients faster, with a slim chance of gaining attention before the end of the month. It has been languishing for several months awaiting Senate action.

The Cures bill also has been hampered by disagreements over funding.

WILL FDA OPPOSITION MUDDY RENEWAL EFFORTS?

Any renewal effort could run into problems, given FDA's opposition to the program's renewal, as well as its expansion.

Agency officials told the Government Accountability Office that they were not sure the vouchers actually incentivized drug development, given the workload involved.

Melmeyer said NORD is working with FDA to resolve outstanding issues about the program's burden on staff. He said both sides' goals are not far off.

Advocates are hoping the program can be made permanent.

Nancy Goodman, executive director of the advocacy group Kids V Cancer, told the Pink Sheet that "a short-term extension would be a shame."

"It would not constitute an incentive for academics or small companies, many of which are doing the most exciting drug development work for pediatric cancers and other pediatric rare diseases," Goodman said. "It would just enable certain companies to reap windfalls for drugs already in development."

A permanent extension of the voucher program could appear in the 2017 user fee reauthorization package.

The prescription, generic drug, and biosimilar user fee programs are advancing toward congressional renewal. Agreements between FDA and industry to continue all three programs have been completed.

POPULAR, BUT LOSING POTENCY?

Since its creation as part of the 2012 FDA Safety and Innovation Act, the rare pediatric disease priority review voucher program has been much more popular than its older sister

targeted at neglected tropical diseases.

Sponsors gaining approval of a drug for what the agency believes is a rare pediatric disease can receive a voucher. The tropical disease program functions in a similar way.

FDA has issued six rare pediatric disease vouchers, its first in early 2014, compared to four tropical disease vouchers.

Orphan product sponsors are excited about the program, in part because vouchers can be sold to others for an infusion of capital for research and development.

NORD president and CEO Peter Saltonstall highlighted the program's financial benefits for sponsors in an email to stakeholders urging them to voice their support of the program.

"This voucher is a powerful economic incentive for pharmaceutical companies to enter the rare pediatric disease drug development arena and has already proven its economic worth," Saltonstall wrote in the email.

The price of a voucher may have reached a short-term price peak, though. United Therapeutics Corp. sold a pediatric voucher to AbbVie Inc. for $350m in August 2015, but Gilead Sciences Inc. appears to have acquired one this year for substaintially less, potentially because of the increasing number available.

The high voucher prices also do not increase the likelihood of approval. Sanofi recently lost the advantage it gained by using a voucher to gain a faster review for its diabetes combination product iGlarLixi, hoping to even its race to market with Novo Nordisk AS's iDegLira after FDA delayed its decision.

Sanofi purchased the voucher for $245m from Retrophin Inc. in May 2015.

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More Pressure On Pharma: UN Report Backs Compulsory Licensing

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The United Nations Secretary-General's High-Level Panel on Access to Medicines has underscored the importance of compulsory licensing as a policy tool for governments to promote access to health technologies under specific circumstances.

The panel's report, made public on Sept. 14, touches on a range of issues including delinking the costs of research and development from the end prices to promote access to good health and intellectual property laws and access to health technologies.

The report notes how life-saving treatments, while under patent protection, can at times be financially unsustainable, specifically referencing how the prices of cancer medicines in the US have nearly doubled from a decade ago, averaging from $5,000-10,000 per month. A February 2016 reference from the Netherlands ministry of foreign affairs also flags the high cost of sofosbuvir.

The report calls for governments to adopt and implement legislation that facilitates the issuance of compulsory licenses; such rules must be designed to "effectuate quick, fair, predictable and implementable" compulsory licenses for legitimate public health needs, and particularly with regards to essential medicines, it says.

MOVING BEYOND EMERGENCY LICENSES

"The use of compulsory licensing must be based on the provisions found in the Doha Declaration on the TRIPS Agreement and Public Health and the grounds for the issuance of compulsory licenses left to the discretion of governments," the report said. It also notes that the Doha Declaration "dispelled the myth" that compulsory licenses should be limited to emergency situations by confirming that governments are free to determine the grounds under which such licenses are issued.

Dr Yusuf Hamied, Cipla Ltd.'s chair and a member of the United Nations Secretary-General's high-level panel on access medicines, told the Pink Sheet that voluntary licenses have resulted in considerable progress in access to medicines at affordable prices in areas like HIV and hepatitis C.

"This should be extended to other areas such as TB and antimicrobial resistance. But when voluntary licenses are not given, countries should decide what is essential for them and enforce compulsory licensing," Hamied told the Pink Sheet from New York.

He referred to recent reports on a German patent court ordering a compulsory license permitting Merck & Co. Inc. to continue to market raltegravir (marketed as Isentress) after Japan's Shionogi apparently rejected its request for a voluntary license.

Compulsory licensing has been a prickly issue with developed nations; the USTR has long kept a hawk eye on India's application of its compulsory licensing law. Earlier this year the US-India Business Council's statement to the office of the USTR concerning the 2016 Special 301 Review raised a storm in India, after the business advocacy organization claimed that the Indian Government had privately reassured that it would not use compulsory licenses for commercial purposes – the Indian government has denied such assurance.

FIGHTING FOR SMOOTHER EXPORTS

Known for his anti-monopoly stand, Hamied said that firms like Cipla will continue to fight against the "excesses" of intellectual property rights such as ever-greening and frivolous patenting.

"We believe that patents should be granted for genuine innovations. Cipla is not against patents; we took out a number of patents on ARVs [antiretrovirals] but did not enforce these … we made it public. We are against monopoly," he said.

He also claimed that Cipla had offered to third world countries its products and technologies "as and when they want to enforce" their own compulsory or voluntary licensing.

"What Cipla will do is to continue to negotiate with pharma companies [for] voluntary licensing and compete with patent holders after the patents are expired," he added.

The UN panel report also recommended that WTO members should revise the paragraph 6 decision – a temporary waiver agreed by WTO members – in order to find a solution that enables a swift and expedient export of pharmaceutical products produced under compulsory license.

"WTO members should, as necessary, adopt a waiver and permanent revision of the TRIPS Agreement to enable this reform," the report said.

It also stipulated that governments and the private sector must refrain from "explicit or implicit threats, tactics or strategies" that undermine the right of WTO members to use TRIPS flexibilities.

"Instances of undue political and commercial pressure should be formally reported to the WTO Secretariat during the Trade Policy Review of members. WTO members must register complaints against undue political and economic pressure, and take punitive measures against offending members," the report said.

Hamied said that he hopes that the proposals put forward in the report would be accepted internationally in the "spirit" in which the final report has been issued.

STOPPING SHORT OF 'EFFECTIVELY AUTOMATIC' LICENSING

It is, however, clear that the panel members had differing views on the compulsory licensing issue.

The report notes how the high-level panel engaged in a robust debate as to whether governments should, in the interests of meeting human rights and public health objectives, be encouraged to implement a system of compulsory licensing in national legislation that is "effectively automatic" by way of its predictability and implementation, provided the specific requirements of the TRIPS Agreement are met.

"While a majority of panel members were in favor of such an approach, a sizable minority were not, because of concerns over the potential incompatibility of such measures with the TRIPS Agreement and the unintended consequences that may result from such an approach. The high-level panel therefore did not reach consensus on this particular issue," details in the report said.

The Panel, nonetheless, suggests that national laws be drafted in a way that facilitates the "prompt and expedient" use of a compulsory license or government use for non-commercial purposes of a patent, including criteria to determine the remuneration for the right holder.

GSK URGES NEGOTIATIONS BEFORE TRIPS

Panel member and GlaxoSmithKline PLC CEO Andrew Witty, in his commentary provided in the report, noted, among other issues, that he recognizes that compulsory licenses can be used legally and that, where they are, fair and efficient compulsory license processes are needed; industry and other stakeholders should also not "overreact" to every compulsory license and treat it automatically as a "no-go area", he said.

Witty, though, said that he fears that any element of "automatic use" of compulsory licenses for medicines would have significant "unintended" consequences.

Under Witty, GSK has pushed for sponsor-driven patent pooling that could nevertheless ensure access for lower-income countries.

"The journey from concept to finished medicine can take up to 25 years. If there is significant uncertainty about returns being available for successful, value-adding products at the end of that period, investors and therefore companies would be much less willing to invest the significant levels of funding required to discover, research and develop new medicines. Innovation would be endangered for patients around the world," he said.

Witty stressed that compulsory licenses should be granted in line with the provisions of the TRIPS agreement and the Doha Declaration – they shouldn't be a routine or automatic element of a country's industrial or health policy, and neither generally be used if there are "good" therapeutic alternatives available at "reasonable" prices.

"If a compulsory license, or any other TRIPS flexibility, is to be pursued, it should be preceded by negotiation," he added. He believes that the report overstates the extent of TRIPS flexibilities.

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Japan Wants EMA To Stay In UK Post-Brexit

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The Japanese government wants the European Medicines Agency to stay in the UK after the country leaves the EU and also the current system of EU-wide medicines regulation to continue to apply there.

The assumption to date has been that, post-Brexit, the EMA will relocate from London to one of the remaining 27 EU member states. Several countries including Ireland, Sweden and Spain have already said they want to host the prestigious EU body. Spain reportedly has identified six cities it says are up to the job.

However, Japan's Ministry of Foreign Affairs says both the UK location of the EMA and the current medicines certification system between the UK and EU should be maintained. "Japanese companies are concerned about the relocation of EU agencies currently located within the UK. Many Japanese pharmaceutical companies are operating in London, due to the EMA's location," according to the statement, which was issued around the time of the recent G20 Summit in Hangzhou, China.

It is up to member states to decide where EU agencies are located. While it is highly unlikely that they would vote to locate a new agency outside the EU, they have never before had to decide what to do in a case such as this where an EU member state hosting an established agency leaves the union. Nothing can be discounted at this stage. Formal exit negotiations have yet to start and no-one would be surprised were the UK to negotiate for the EMA to stay in London.

> "Many Japanese pharmaceutical companies are operating in London, due to the EMA's location."

Japan says it wants to see full transparency around any Brexit talks and for there to be sufficient transition time allowed for any major policy and regulation changes.

EMA TO LOSE EMER COOKE, ITS HEAD OF INTERNATIONAL AFFAIRS

In the meantime, the EMA has announced that its head of international affairs, Emer Cooke, is leaving the agency for a high-level post in medicines regulation at the World Health Organization in Geneva, Switzerland. The departure of Cooke, a high-profile figure at the agency and a familiar face and regular speaker on the international pharmaceutical regulatory conference circuit, will be felt at the agency. She has held the key post of head of international affairs at the EMA since 2013. She has worked at the EMA since 2002, during which time she has also served as head of international and European cooperation and head of inspections.

Cooke, originally from Ireland, join the WHO in mid-November as head of regulation of medicines and other health technologies in the Essential Medicines and Health Products Department. EMA Executive Director Guido Rasi said Cooke had made "a significant contribution to the global recognition of the EU network activities" and that he was confident she would "continue to further develop the close collaboration between EMA and WHO".

Cooke described the June 23 vote by the UK to leave the EU as "a decision that affects a lot of the staff of the agency, personally and professionally". Speaking at the end of June, she said: "You sort of don't believe it." Cooke stressed, though, that "we will continue with business as usual – no immediate changes apart from the emotional shock."

The EMA's head of portfolio board, Agnès Saint-Raymond, will take over on an interim basis pending the appointment of a new head of international affairs.

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India Moves To Replace Animal-Based Tests In Eye, Skin Studies

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India's ministry of health and family welfare has issued draft rules outlining the use of non-animal test methods as an alternative in dermal and ocular toxicity studies.

In a notification, dated Aug. 23, but uploaded on Sept.12 on the Central Drugs Standard Control Organization website, the government says that in the case of dermal toxicity studies, the initial toxicity study may be carried out by "validated non-animal alternative tests", where such alternatives are available; in rabbit and rat studies, daily topical application of the test substance in its clinical dosage form "should be done", the notification adds.

In the case of ocular toxicity studies (for products meant for ocular instillation), Schedule Y of India's Drugs and Cosmetic Rules 1945 notes, among other specific requirements, that the initial single dose application should be done to "decide the exposure concentrations for repeated-dose studies and the need to include a recovery group". The ministry's latest notification now adds that: "Such initial studies may be carried out by validated non-animal alternative tests, where such alternatives are available." Schedule Y pertains to the guidelines and requirements to import or manufacture new drugs for sale or to undertake clinical trials in India.

Animal rights groups have long opposed what some of them term as the "cruel and crude 1940s-era methods" Draize tests – John Draize, a pharmacologist with the US Food and Drug Administration originally developed a method for testing eye and skin irritation using rabbits. Though widely accepted, the test has been controversial from the ethical standpoint since it entails using restrained and live rabbits. People For The Ethical Treatment Of Animals (PETA) claims that the rabbits often suffer from ulcers, bleeding, and even blindness and aren't given painkillers during the tests. PETA India has been pressing for the introduction of non-animal methods for skin and eye irritation and corrosion, which have been validated internationally. PETA claims that in addition to being more humane, non-animal testing methods are more relevant, less expensive, and faster than tests on animals.

"IN VITRO METHODS NOT SUITABLE"

However, Sun Pharmaceutical Industries Ltd., which has expressed its reservations against efforts to mandate the alternative tests in ocular and dermal toxicity studies, told the Pink Sheet that considering "no one" in India has the "infrastructure and feasibility" for implementing such alternatives, the implementation of these alternative tests could take at least three years.

"The pre-requisites for these alternatives include procurement of instruments, establishment of infrastructure and development of expertise along with in-house standardization and validation of test and demonstration of proficiency," Sun explained.

It also noted that no single alternative test can replace the in vivo tests completely, as each test has some limitations. For example, fluorescence leakage is suitable for only water soluble compounds; the ARE-Nrf2 Luciferase test method can give false negative results if the compound is highly cytotoxic.

India has issued draft rules to replace animal tests in eye and skin studies.

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"Most of the *in-vitro* methods are not suitable for solids/aerosols/creams/gels and other viscous formulations. Each test has its own sensitivity/specificity. Besides, if the alternative test does not give conclusive results, then in-vivo test is to be used. Hence, based on the characteristics of the molecule/product, we believe the option of performing *in-vivo* test should also be kept in the revised guideline," Sun said.

It's not immediately clear whether the alternative testing requirements could impact any of Sun's R&D plans or the ongoing projects of Sun Pharma Advanced Research Co. Ltd. (SPARC) that include a topical minocycline and a once daily brimonidine. SPARC is the listed spin-off R&D arm of Sun Pharma.

REPRESENTATIONS

The Aug. 23 notification comes against the backdrop of certain representations made to the Drugs Controller General of India to amend Schedule Y, replacing the Draize test with alternative non-animal models. The DCGI had subsequently constituted a committee chaired by Dr Y K Gupta, Professor and Head, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi.

The committee, with certain experts and representatives from PETA, examined the issue at its meetings in May and July this year; the panel also sought comments from various stakeholders – five organizations including Sun Pharma responded.

Details in the minutes of the 73rd meeting of India's Drug Technical Advisory Board in August, indicated that all the organizations that responded supported replacing the Draize test with non-animal test methods, except for Sun. The DTAB is the highest technical body under India's Drugs and Cosmetics Act.

Sun, at the time, sought that alternative tests not be mandated but that *in vivo* tests also be allowed for such pre-clinical toxicolog-

ical tests considering the limitation of *in vitro* tests based on "molecule characteristics". Among other arguments, Sun also claimed that it does not have the capability or capacity *for in vitro* alternate methods and such capacity building could take at least three years.

The committee led by Dr Gupta, however, held that the Indian regulatory system should "adopt [a] progressive nature" in embracing alternate methods to animals in toxicity testing as and where possible; these methods should be validated as sufficient alternative for "equal predictability of potential toxicity" of pharmaceutical products, it added.

It noted that it was important to consider whether a single *in vitro* test, as stand-alone, is acceptable or a battery of tests are required for reliable assessment and under what circumstances, such single or multiple *in vitro* tests, will not be acceptable as alternate to the Draize test.

"The applicant of [a] new drug should be encouraged to make application to the regulator for conduct of *in-vitro* alternate methods in place of Draize test and if the regulator has no specific reservation/requirement, may accept it. The intent should be to gradually phase out the Draize test by replacing it with *in-vitro* tests," the committee said.

It noted that the Draize test should, in the interim, be accepted for two years, during which period, all testing laboratories should develop the capacity for *in vitro* testing facilities and validate them. After one year, a "stock taking" of progress in capacity building should be done.

The committee, though, said that in rare situations where an alternate test is not acceptable for acute dermal/ocular toxicity testing and with specific reasons and the Draize test is asked for, a set of specific principles should be applied. These include that a known molecule with known irritant properties/adverse effects should not be used and that the test should be done starting with the least possible concentration.

Based on the recommendations of the committee, amendments to Schedule Y of the Drugs and Cosmetics Rules, 1945 were proposed and these were endorsed by the DTAB, details in the minutes of the August meeting added.

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China Proposes Many New GLP Provisions For Pharma

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The China Food and Drug Administration is seeking feedback on proposed revisions to its rules on good laboratory practice (GLP) that are being updated to improve the quality of non-clinical studies for assessing the safety of drugs.

The revised GLPs proposed by the CFDA comprise "many new provisions and new or enhanced requirements," said Shaoyu Chen, a partner and managing director at the Shanghai office of law firm Covington & Burling.

The revisions relate to GLP regulation and, as such, carry more weight than a guidance, Chen told the Pink Sheet.

"Companies should submit comments, monitor the development, and make sure that [they follow] the new requirements after this proposed GLP is finalized and promulgated," he said. The deadline for submitting public comments on the proposals is Oct. 18.

GLP regulations set out specific requirements for how animal studies should be conducted in order to ensure the quality of the data generated for drugs and to protect animal welfare, Chen noted.

The revised GLPs comprise the requirements the CFDA wants research organizations to comply with when they perform non-clinical studies to assess a drug's safety such as testing for toxicity, immunogenicity and carcinogenicity.

The proposed GLPs are contained in draft document that the agency released for consultation last month. Once finalized, they will replace GLP rules that were issued in 2003. Chen noted that China has recently proposed and amended several of its good practice guidelines and regulations (good clinical practice, good manufacturing practice and good supply practice) in a bid to raise drug development standards in the country.

INSPECTIONS, FACILITIES AND STAFF

The draft GLP document deals with, among other things, the inspections the CFDA carries out on research institutions and the repercussions they face if they violate non-clinical study rules. For example, depending on the violation, institutions may be given the chance to take corrective actions or they might have their certification withdrawn.

The document also covers requirements relating to facilities, equipment and laboratory animals. It talks about the layout of facilities and the need to prevent cross-contamination between test systems, test substances and wastes. It says that institutions must meet the research needs of an animal facility with regard to environmental conditions relating to temperature, humidity, air cleanliness, ventilation and lighting.

The draft document also says that computerized systems for data acquisition, transmission, storage, processing and archiving should be verified. It adds that electronic data must have a complete audit trail and electronic signatures in order to be regarded as the original data.

The proposed GLPs deal with professional qualification expectations for staff that conduct non-clinical studies and their responsibilities.

It also covers the standard operating procedures that research institutions should adopt to ensure the quality and integrity of their data.

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Korean Health Tech Blueprint Highlights Precision, Regenerative Medicine

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In a major policy and regulation initiative, South Korea has released a wide-ranging strategic health care industry development strategy for the 2016-2020 period, outlining a raft of new policy plans in various sectors including pharma, precision and regenerative medicine, and medical devices.

The latest measures, which mark the country's first comprehensive plan covering the overall health care industry, form part of a series of measures unveiled to upgrade the global competitiveness of South Korea's domestic biotech and healthcare industry.

"As convergence within the healthcare industry and with other industries such as IT is accelerating, it has become necessary to devise a strategy that looks into the overall industry," explained the Ministry of Health and Welfare.

The government said the aim is to come up with strategies for each health care sector in line with its maturity and operating conditions. For instance, for precision and regenerative medicine, as well as ICT (information communications technology)-converged healthcare and medical services - which are all still in their early stages - the objective is to improve laws and regulations to establish a growth base for these new industries.

In other areas such as medicines, medical devices and cosmetics, which are facing fierce competition globally, the government will provide a range of fiscal support measures in R&D, tax incentives and exports to nurture leading global firms.

Through the measures, the government's overarching aim is to boost the nation's healthcare industry exports to KRW20tn ($18.2bn) by 2020 from KRW9tn in 2015, and to expand the number of related jobs to 940,000 by 2020 from 760,000 in 2015.

PHARMA SECTOR

In the pharma field, South Korea aims to develop 17 novel global drugs by 2020 from two in 2016, to create two top 50 global pharma firms (by sales) in 2018 from zero in 2015, and to have developed 10 biosimilars by 2020 from five in 2015.

South Korea aims to develop 17 novel global drugs by the end of 2020 from two in 2016, to create two top 50 global pharma firms by the end of 2018.

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One aim is to remove barriers to entry in global markets through customized export support, and another is to increase domestic self- sufficiency in vaccines, which stands at just 39% at present.

The other main pharma measures are as below.

- **Beef up strategic R&D support to next generation and cutting edge medicines.** R&D productivity will be improved by providing support for the transfer of basic research at universities, hospitals and public research institutes to pharma firms and to commercialize this.
- **Expand R&D support to novel drugs and promising areas.** Expand cooperation among various ministries to develop South Korea-originated novel global drugs such as novel antibodies.
- **Focus investment in areas that have potential for first-in-class drugs.** South Korea will support neuroscience and metabolic diseases/diabetes this year.
- **Support development of novel drugs based on open innovation** among domestic pharmas, universities and research institutes in four serious disease areas (cancer, cardiovascular, cerebrovascular and rare diseases).
- **Support development of vaccines to overcome infectious diseases.** With a goal of localizing vaccines and reducing national medical cost, the aim is to invest in public use vaccines and those with cutting edge technology.
- **Boost infrastructure to deal with disasters and set up a public vaccine development and support center** within the Korea Centers for Disease Control and Prevention. This will seek to create a global partnership-based technology development fund to develop novel drugs and medical devices.
- **Obtain global technological competitiveness and globalization of innovative pharmas** by expanding support for joint global research projects with foreign universities and companies.
- **Support localization of production and distribution operations of domestic pharmas when they advance abroad.** A pharma industry export consultative body will be set up to partially cover the cost of establishing local import and distribution firms.

PRECISION MEDICINE SECTOR

In the therapeutics area, another key area of focus of the plan will be novel targeted therapies based on the collections and use of genomic and other data, and using ad-

The aim is to raise the average five-year survival rates for three major progressive cancer types (lung, gastric and colorectal) to 14.4% by 2025 from 8.4% in 2014.

vanced information technology systems. Detailed plans for precision medicine technology development will be drawn up as a national strategy project.

The government says it intends actively to use genomic and medical service big data to help overcome rare and incurable diseases, and as a result expects to develop customized health management through use of targeted therapies.

It aims to raise the average five-year survival rates for three major progressive cancer types (lung, gastric and colorectal) to 14.4% by 2025 from 8.4% in 2014.

There is also an expectation that national medical costs can be reduced by applying the most appropriate therapy for each patient to minimize side effects and other unnecessary treatment.

South Korea already has the basic infrastructure and technology for a precision medicine system, but lacks state-level support as well as investment and competence. It is weak in connecting and sharing resources such as genomic, medical and clinical trial data owned by individual institutions, limiting its use in development of novel drugs, the plan concedes.

Other major measures include those below.

- **Create a Korean Precision Medicine (KPM) cohort** by collecting data from at least 100,000 people (both healthy and diseased) and enable access to these data for R&D and commercialization.
- **Set up a platform to link and share precision medicine resources.**
- **Develop and provide precision medicine services.** The plan is to analyze and diagnose cancer-related genomes as well as to develop treatment methods.
- **Obtain genome data from 10,000 patients suffering from three major progressive cancers** (lung, gastric and colorectal cancer) and conduct precision medicine anticancer clinical trials to diagnose and develop treatment methods.
- **Create a database from genomic and clinical trial information** and provide this to domestic and foreign pharma firms through an "integrated precision medicine information system" and support the development of customized anticancer therapies.
- **Develop clinical decision supporting system** using artificial intelligence.
- **Develop and substantiate health management service programs** for mobile devices.
- **Draw up a special legislative act for precision medicine** to create a research base and prop up technology development.

REGENERATIVE MEDICINE SECTOR

Through a range of measures designed to rejuvenate the area of regenerative medicine, the South Korean government expects to expand treatment opportunities for patients with rare and incurable diseases. Helped by prompt systems within hospitals, it aims to shorten the time between clinical development and application to patients to within three months, from two to five years at present.

South Korea is seen as having strong regenerative medicine technology but weak regulations that could speed up its application, and a number of measures are outlined in the new blueprint to improve the rules, including the enactment of an advanced regenerative medicine law.

- **Legalize a system that enables qualified medical institutions to conduct regenerative medicine treatments** before these therapies are formally approved under the Pharmaceutical Affairs Act.
- **Make proactive investment** in R&D of cell therapies and "customized" organs.
- **Support R&D of next generation cell therapies to maintain and expand market competitiveness.** Support development and clinical research of technology that strengthens the therapeutic effect of adult stem cell therapies, and support the development and clinical research of targeted anticancer therapies using immune cells.
- **Support development of technology-convergent cell therapies that inhibit disease occurrence** by using genetic scissors technology.
- **Develop a roadmap to reduce the cost of regenerative medicine therapies** and encourage their public use.
- **Through a preliminary feasibility study, support development of tailored artificial organs** via 3D printing.

The hope is to slash the time between clinical development and patient application of new regenerative medicines to within three months, from two to five years at present.

- **Build regenerative medicine infrastructure and strengthening global leadership.** The government will operate a state-owned stem cell regeneration center to secure a basis for developing, providing and supporting clinical use stem cells.

MEDICAL DEVICE SECTOR

As well as these various areas concerning a range of therapeutic approaches, the new plan sees medical technology as another key part of the overall strategic approach to healthcare. To help South Korean firms enter global markets, the government aims to boost competitiveness through collaborations with leading international firms.

It says it will support small- and medium-sized domestic companies to reach strategic

alliances and will seek to attract investment from leading global medical device firms. Customized support for promising technology and products will be strengthened and outstanding companies in 10 areas including imaging, bioinstrumentation and in vitro diagnostics, will be selected for support.

Other major strategies include those listed below.

- Expand translational research and support for clinical trials to commercialize IT and biotech convergence devices such as high-risk therapeutic devices and materials, as well as medical robots.
- Introduce a phased approval system to rapidly approve cutting edge and convergence medical devices, as well as a system that can speed up the use of 3D-printed customized devices.
- Support comparison and verification of the performance of domestic medical devices to improve their international credibility and brand awareness.
- To advance distribution and management, introduce a unique identification code system for medical devices next year similar to that already used for drugs. The system will enable better management of information on device manufacturing, distribution and usage.

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Digital Marketing: Health Care Brands' Window Into Consumers' Lives

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"Psychographics" are better windows for forming bonds with consumers via digital marketing than age, socio-economic status, diagnosis and other broad data points that typically drive OTC drug firms' advertising, says a health care industry marketing and e-commerce consultant with C2B Solutions.

"Digital marketing is really a platform to integrate yourself with the consumer's life and form an ongoing relationship, but that is a whole different mindset from the classical marketer," said Brent Walker, executive vice president and chief marketing officer for the Cincinnati consultancy.

Companies should think in terms of a person's psychographics – values, attitudes, lifestyles, personalities. "Basically, who you are as a person," Walker said in an interview.

However, while firms in industries like banking and finance are targeting marketing to integrate their brands with consumers, most OTC drug and wellness product companies keep consumers online at arms-length, he suggested.

"A pitfall for marketers whether it is an OTC or Rx, they may define the product, may define the world by their product or category, as if the consumer is walking around thinking of their category, like a walking disease state. That's a huge 'watch-out' because they're not thinking in those terms," said Walker, previously a Procter & Gamble Co. health care marketing executive.

Psychographics tend to drive purchasing decisions, he said, noting five general types (*see table, p. 21*).

Segmenting consumers based on psychographics allows health care firms to customize communications for like-minded consumers based on their motivations and preferences. This outreach can be through a brand's website, e-commerce sites like Drugstore.com and Amazon and self-care sites such as WebMD as well as social media and email.

"Outreach should vary by segment types, too. Some segments want emails more than others. Some segments are more appreciative of text messages. Phone calls/interactive voice response work for other segments. The optimal frequency of communications is different for different segments, as is the point of message fatigue," Walker said.

Many marketers also continue to view digital narrowly, as a playground for younger consumers.

"I think most of the fast-growing cohorts out there are baby boomers, even some of the greatest generation types. Some of them are growing faster than anyone else in digital [because they are going there] to keep track of family members" on social media sites, he said.

Digital marketing spending is expected to grow at a compounded annual growth rate of 9% through 2020, fueled by the increased use of smartphones and less expensive internet services, accord-

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C2B Solutions Psychographic Segmentation Model

% OF CONSUMERS	SEGMENTS AND CHARACTERISTICS
13%	**Direction takers:** prefer to be told by health care professionals what they need to do; clinicians are the experts in their eyes; like to cut to the chase and do not like to be asked a lot of questions. This segment reflects the way health care traditionally has been delivered.
18%	**Balance seekers:** proactive- and wellness-oriented, but downplay the role of health care professionals; prefer options and suggestive approaches and open to alternative medicine rather than being given an already mapped out route to wellness and directive health care.
27%	**Willful "endurers":** independent and the least proactive about their health; live in the moment and do not focus on long-term benefits or consequences. The challenge is to find ways to motivate them toward adopting healthy behaviors through immediate gratification.
18%	**Priority jugglers:** tend to be less proactive and engaged with their health care because they put other responsibilities ahead of personal health; however, proactive in managing their family's health; may require a higher level of interaction to keep them focused on their own healthy behaviors.
24%	**Self-achievers:** the most proactive- and wellness-oriented group; goal- and task-oriented, appreciate measures to gauge progress in their efforts; are the most willing to spend whatever it takes to be healthy.

ing to market research and consulting organization Hexa Research. Hexa said in a July release that the biggest global spenders in the area include Johnson & Johnson, L'Oreal SA and P&G.

TRACKING PREFERENCES, LEVERAGING BRAND APPEAL

One means of understanding how consumers think and shop is accessing purchase histories and reviews on e-commerce and brands' sites. This information comes from services such as Google's DoubleClick, which tracks web pages consumers have viewed and products they purchased and provides data to advertisers. Programs like Google Analytics can measure consumer behavior on a brands' site, such as features clicked on the most.

Also effective for gleaning data are quantitative studies and surveys, which generate information from consumers willing to participate while visiting a website or in-store kiosk or to answer in an email.

"To hear the segments talk about health, products and personal journeys using their own words and through their own motivations and priorities" is effective, Walker said. C2B and other consulting firms can conduct those surveys for clients.

Companies can use that data to develop content, messaging, coupons and other outreach.

Once a person's past behaviors and buying history are known, "recommend complementary products that go with the product they are buying," Walker said.

For example, if consumers buy antihistamines online, rather than hammering them with ads for the same products, firms can promote products for other issues associated with allergies, such as can featuring ads or recommending products for dry eye or nasal congestion.

Non-complementary products still within a person's psychographic segment are another option.

"You can say, 'this may not have anything to do with what you're buying right now, but based on what we know about you as a person, you may be interested in this'," Walker said.

For example, if purchasing histories or input from surveys indicate consumers are fitness-focused, a marketer can promote fitness-related nutritionals.

Walker noted the utility of pop-up and banner ads, recommending their use only to supplement and complement existing outreach.

"When this all started out, this was the primary way to advertise products online, but people got ticked off because they were annoying as all heck." However, "if I do get a banner ad for something that I'm interested in, then because it complements my experience," it can help reinforce a connection to the brand, he said.

Walker said firms also should "reframe" their brands to capture new consumers with a different way of viewing the product.

While at P&G, Walker worked on transforming the Metamucil brand's image from a product seen as "an old person's laxative" to one that provides a fiber benefit, he said.

"So now [the brand] has claims on lowering cholesterol, appetite suppression, making you feel full. So P&G can say, 'OK, if you want a wellness regimen and doing preventive approaches, you might also like this,' then point to fitness or other nutrition products, like supplements."

P&G in 2015 also promoted Metamucil's Meta supplement products with health care company UnitedHealth Group Co. P&G sent to United members with high cholesterol educational material and incentives to purchase the Meta line of supplements.

P&G spent $4.6bn on advertising in 2014, according to Ad Age's annual Leading National Advertisers report, published in July 2015. P&G announced in August that it will reallocate some of its digital investment online, pulling back on certain targeted Facebook campaigns, for example, and placing more power behind mobile.

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Teva Seeds OTC Growth Synergies With Former Allergan Business

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If Teva Pharmaceutical Industries Ltd. wasn't sufficiently enthused about the OTC drug space with the launch of a consumer health joint venture with Procter & Gamble Co. in 2011, its recent addition of Allergan PLC's generics business flipped the switch.

"I think we are more excited about the OTC [space] today than we have ever been before due to the synergy we see in the business," said Sigurdur Olafsson, president and CEO of Teva's Global Generic Medicines Group. He spoke during a Sept. 9 New York investor briefing on integrating Allergan's generics business acquired in a $40.5bn deal that closed in July, a year after it was announced.

The specific source of the excitement, said Olaffson, is the firm's opportunity to compete in the US OTC drug market now that the Allergan's generic nonprescription products are under its roof.

Framing his comment with "last but not least," he said, "We haven't been playing in the US OTC business up until now. I think there is an opportunity. This is obviously a fast-growing business."

Olaffson noted another reason for Teva's OTC sector excitement – the firm is first-to-file abbreviated new drug applications with FDA to make generics of *Nexium 24HR*, Pfizer Inc.'s OTC 20mg esomeprazole proton pump inhibitor, and of Sanofi's *Nicoderm CQ* nicotine-replacement therapy transdermal.

An additional opportunity for Teva's OTC play gained from Allergan is manufacturing generics of nonprescription brands that other firms market, including private label versions of RB's *Mucinex* guaifenesin-containing expectorant and decongestant line for Perrigo Co. PLC.

"This is one of the hardest generic drugs to develop. I think this is just one example of where there is a synergy between the generic development and the OTC," Olaffson said.

Perrigo would attest to the difficulty of making guaifenesin products. The firm's multiple launches of private label Mucinex products that it made were beset by manufacturing problems before it hired Allergan to supply the line.

NICHE, NOT CORE

However, Olafsson tempered expectations about the size of the business in the US by emphasizing that private label OTCs generate lower margins than branded products and that Perrigo is "the giant gorilla" in the space.

"It's not our core business. We are not, in any way, competing with Perrigo at this point in time," he said.

"We want to see this as a niche opportunity. … It's less than $100 million of our revenue today, so it's still a relatively small business, but it's opportunistic business we are thinking about," the CEO added.

Outside the US, Teva already had one foot in the OTC space through the PGT Healthcare JV before extending its nonprescription footprint with Allergan's former products.

The firm agreed with P&G to keep its new OTC assets separate from the JV, though Teva sales staff will represent products from both entities. PGT does not operate in the US.

"There's still a synergy with the joint venture. We will have one sales force as a front to the customers. But this was the right decision for the company and allows us to integrate it better into the Teva business," Olaffson said.

Teva's products that are under PGT's roof also are helping fuel its OTC enthusiasm. In addition to P&G consumer health brands such as the *Vick's* cough/cold line and the *Swisse* vitamins and supplements that the JV markets in Europe, it distributes Teva's branded generics, *Teva* in most markets and *ratiopharm* in Germany.

MORE HERE, NEW THERE

Another Teva consumer health brand available in Europe is *Sudocrem* diaper rash ointment. "I didn't know this was needed, but this is a very well-known brand in that indication," Olafsson added.

OTC sales in Russia of Troxivan, a troxevasin gel for treating varicose veins, are another addition from the Allergan deal.

Erez Israeli, Growth Markets president and CEO for Teva, said the firm currently is No. 3 in Russia's pharma market with a portfolio that reached 300 products following the Allergan deal. With more than 1,000 representatives in the country, "we have a very significant commercial presence," Israeli said during the investor briefing. "Russia is a big country that requires base in every one of those provinces."

A big market, but also one with a big reliance on out-of-pocket spending on pharma products, Israeli said the Teva brand frequently is in print and TV ads to "help us also to generate demand on both OTC and the prescription product."

Meanwhile, in Germany ratiopharm has "tremendous brand equity" that Teva already was building on since its 2010 acquisition of the brand, but in the firm is new to Bulgaria with Allergan's former products. "Our presence was zero, okay, prior to this acquisition, and we've gone from there to number one," Israeli said.

From the editors of the Tan Sheet. Published online September 13, 2016

MORE TEVA PERSPECTIVES

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These articles offer additional coverage from the company's investor briefing:

"Teva's 'Key Ingredient' For Growth: Biosimilars" — Scrip, 13 Sep, 2016.

"Heated Drug Pricing Debate Fanned By Election, Teva's Olafsson Says" — Scrip, 12 Sep, 2016

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FDA Neurology Clinical Team Leader Departure May Be Mountain Disguised As Molehill

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Like most controversies today, it started with a tweet.

"Seems like Ron Farkas is no longer at the @US_FDA cc $SRPT" Jenn McNary, one of the most active Duchenne Muscular Dystrophy patient advocates and a mother of a son with DMD, wrote on Sept. 13 using the stock ticker symbol for Sarepta Therapeutics Inc., the sponsor of eteplirsen.

The reaction on social media was fast and furious: reporters and investors attempted to confirm with FDA and Parexel – the rumored new employer of Farkas – that the reviewer had indeed left the agency.

Farkas was Division of Neurology Products clinical team leader who conducted the review of Sarepta's DMD drug eteplirsen. His review was overwhelmingly negative and concluded that not only was there not substantial evidence of an effect from eteplirsen but there was no evidence at all.

McNary's tweet in turn led to Wall Street speculation and stories confirming Farkas had left FDA and that it was a positive development – if not confirmation – that eteplirsen will get accelerated approval. The application has survived bumps at FDA but remains a possibility for an accelerated approval.

But reading the tea leaves of the Farkas departure solely as another piece in the up-or-down decision on the Sarepta drug misses a potentially broader significance to the event. There are other messages and reverberations that may last longer.

PERSONAL ENMITY TOWARDS REVIEWERS

The first is the personalization of enmity toward an FDA reviewer. Farkas was painted as enemy number one for what some believed was an obstructionist position on the eteplirsen application for a deadly disease in young boys. Farkas has been negative on other recent applications. He reviewed BioMarin Pharmaceutical Inc.'s DMD drug drisapersen that was rejected by FDA and probably had an important role in FDA's decision to refuse-to-file PTC Therapeutics Inc.'s application for ataluren.

Farkas also was negative on Merck's sleep drug suvorexant that led to a big write-up in the New Yorker titled "The Big Sleep." But that's not always the case. He supported approval of Vanda's non-24 sleep drug tasimelteon for the blind that was approved by FDA.

Removing emotion from the case of eteplirsen, Farkas applied the FDA's long-established regulatory standards to the review and made it very clear that the application fell well short of the threshold for approval in his opinion as primary reviewer.

Tough standards come into conflict with applications for life-threatening conditions at FDA: it is part of the territory.

For many reasons, though, the eterplirsen application reached an almost unprecedented level of political and patient sensitivity. Therefore, Farkas' position as lead reviewer and regulatory determination were magnified. What reviewer will want to take on an application like eteplirsen in the future?

NOT FARKAS' CALL TO MAKE

Lost in the focus on Farkas is the fact that Division Director Billy Dunn and Deputy Director Eric Bastings both expressed the same position as Farkas regarding the eteplirsen application. Office of Drug Evaluation 1 Director Ellis Unger appeared to be of the same mind as well given some of his comments at the panel meeting, but it was less clear.

And if an unprecedented level of regulatory flexibility were to be applied to the filing in order to reach an approval decision, it will be done by several layers above Farkas – that was always going to be the case.

The final sign off decision will fall to Unger or could escalate – unlikely but possible in this unusual case – to CDER Director Janet Woodcock, who opened the door for an accelerated approval pathway for eteplirsen during her presentation at the eteplirsen panel review.

Put another way, it was not Farkas' call to make despite the perception that he was the implacable roadblock to the application.

BOLSTERING REVIEW MORALE

The second issue: this is what the start of a decline of a peak approval climate looks like. Anyone who watched the April 25 advisory committee review of eteplirsen or who has followed Sarepta can tell you this was a brutal review. And the pressure on the neurology division to approve an application for DMD – particularly eteplirsen – has not been lost on other reviewers in different divisions.

In other words, everybody is watching this application but FDA reviewers are watching the eteplirsen outcome too.

If a myth or storyline develops that Farkas left FDA because management overruled him due to external pressure, that would create a significant problem for FDA internally. Senior FDA officials have worked tirelessly and successfully to remove that distraction and create an almost peerless period of pro-innovation, approvals, cutting edge regulatory science and efficiency.

The risk is that others could follow Farkas out the door, or worse stay on at the agency demoralized and perhaps resentful and fretful of being overridden from management above.

Impossible? No. That is what happened in the nadir of the FDA drug approval process four decades ago – two decades before Woodcock even joined the agency. A general perception first within FDA and then generally in the public of too much bending in favor of applications and industry-bias by FDA managers led to a general collapse of morale and Congressional hearings.

PREVENTING A TOXIC REVIEW CLIMATE

Sarepta has collected many Congressional supporters for its application. So a negative response from Capitol Hill to an eteplirsen approval is not likely. What is dangerous is a sense at the working review levels that management is pushing too hard for approvals. That story – true or false – can be toxic to the NDA review environment.

The Neurology Division's portfolio of diseases includes some of the most high-profile diseases for which there is major unmet need: Alzheimer's, Parkinson's disease, Huntington's disease, multiple sclerosis, epilepsy, migraine, muscular dystrophy, ALS, narcolepsy.

Now that division has lost a senior reviewer at a time when FDA is having great difficulty recruiting young neurologists to staff the division. CDER Director Janet Woodcock has publicly lamented the fact that newly minted neurologists out of medical school can make as much as an FDA Center Director.

The truth is no one at this point know why Farkas left. His departure and the eteplirsen review may be completely unrelated or a direct cause and effect. But keep watching to see if something bigger may be brewing here.

From the editors of the RPM Report. Published online September 13, 2016

FDA's NDA And BLA Approvals: Yosprala

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				
Aralez	*Yosprala* (aspirin/omeprazole)	Proton pump inhibitor layered around a pH-sensitive coating of an aspirin core for once-daily use for secondary prevention of cardiovascular disease in patients at risk for aspirin-induced ulcers	S	9/14/2016
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		

FDA's ANDA Approvals

SPONSOR	ACTIVE INGREDIENT	DOSAGE; FORMULATION	APPROVAL DATE
Impax	Choline fenofibrate	EQ 45 mg and EQ 135 mg; delayed-release capsule	9/7/2016
Versapharm	Voriconazole	50 mg and 200 mg; tablet	9/7/2016
Taro	Naftifine HCl	1%; topical cream	9/8/2016
Versapharm	Fluocinol	0.01%; otic oil/drops	9/9/2016
Amneal	Lacosamide	50 mg, 100 mg, 150 mg and 200 mg; tablet	9/9/2016
Glenmark	Lidocaine	5%; topical ointment	9/9/2016
Flamingo	Piroxicam	10 mg and 20 mg; capsule	9/9/2016
Rising Pharm	Doxercalciferol	0.5 mcg, 1 mcg and 2.5 mcg; capsule	9/12/2016
Ajanta	Aripiprazole	2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg; tablet	9/12/2016
Avanthi	*Lomaira* (phentermine HCl)	8 mg; tablet	9/13/2016
Glenmark	Diclofenac sodium	3%; topical gel	9/13/2016

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation	Anesthetic and Analgesic Drug Products; Drug Safety and Risk Management; Pediatric	Sept. 15-16
Naloxone products intended for use in the community, specifically: the most appropriate dose or doses to reverse effects of life-threatening opioid overdose in all ages; the role of having multiple doses available in this setting; criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and labeling to inform this decision if multiple doses are available	Anesthetic and Analgesic Drug Products; Drug Safety and Risk Management	Oct. 5
Selection of strains to be included in an influenza virus vaccine for the 2017 southern hemisphere influenza season	Vaccines and Related Biological Products	Oct. 13 (teleconference)
Serenity Pharmaceuticals' desmopressin 0.75 mcg/0.1 ml and 1.5 mcg/0.1 ml nasal spray for treatment of adult-onset nocturia	Bone, Reproductive and Urologic Drugs	Oct. 19
Updates on research programs in the Laboratory of Immunobiochemistry of the Division of Bacterial, Parasitic and Allergenic Products in CBER's Office of Vaccines Research and Review (open session); intramural research program reports and recommendations on personnel staffing decisions (closed session)	Allergenic Products	Oct. 27 (teleconference)
Cempra Pharmaceuticals' solithromycin capsules and injection for treatment of community-acquired bacterial pneumonia	Antimicrobial Drugs	Nov. 4

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