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Trump Makes A Nasty News Day For Pharma – But What Will It Really Mean?

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President-elect Donald Trump took another swipe at prescription drug pricing and challenged the biopharmaceutical industry's reliance on ex-US tax havens during his first post-election press conference Jan. 11.

Trump's high-profile comments sparked concern in the industry and on Wall Street, which sent drug stocks falling (*see chart, p. 4*). The general downturn erased the gains made after the presidential election, when drug stocks rose on investor relief that industry had escaped a vigorous drug pricing agenda under Hillary Clinton.

It was not the first time Trump has mentioned government price controls for drugs, but the comments are notable because it shows he is intent on keeping the industry on alert. He continues to view drug pricing as a populist issue and industry as a punching bag.

"We have to … create new bidding procedures for the drug industry because they're getting away with murder," Trump said.

Pharma has "a lot of lobbyists and a lot of power and there's very little bidding on drugs. We're the largest buyer of drugs in the world and yet we don't bid properly and we're going to start bidding and we're going to save billions of dollars over a period of time."

DEMOCRATIC IDEAS

Although Trump has offered no specifics, industry worries he is referring to a plan to allow HHS to negotiate drug prices directly with manufacturers on behalf of the Medicare Part D program, an idea that Democrats have supported and the pharma industry has lobbied against for more than a decade.

The law creating Part D specifically prohibits HHS from direct price negotiation so a change would have to be made through legislation.

However, Republicans in Congress have consistently opposed such a bill. Detractors point out the Congressional Budget Office has concluded that direct HHS negotiation would not save the program money because there is no national Medicare formulary that could be used as negotiating leverage. Industry also frequently argues that individual Part D plans already negotiate pricing with manufacturers.

Some ways around the national formulary issue have been discussed in Democratic policy circles. For example, the Obama Administration has explored a process of binding arbitration in which manufacturers and HHS would agree to accept the decision of a third-party arbitrator on the appropriate price for high cost specialty drugs in Part D.

A lack of detail about Trump's plans makes it hard to know how concerned the

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Biologic Product Naming: US FDA Sticks With Suffixes 'Devoid Of Meaning'

http://bit.ly/2iPTbiE

Final guidance adds new factors for biosimilar and innovative sponsors to consider in developing distinguishable suffixes for nonproprietary names but FDA is unswayed by calls for meaningful suffixes derived from license holder's name; timing of retrospective application to previously approved products remains in question.

Global Pharma Guidance Tracker – December 2016

http://bit.ly/2jrBdnl

Stay up to date on regulatory guidelines from around the world, with the Pink Sheet's Guidance Tracker.

Training For 'Huge' EU Clinical Trials Portal And Database On Track For 2017

http://bit.ly/2j7XnLV

"Thousands and thousands of people" will be using the EU clinical trials portal and database after it goes live late next year and the European Medicines Agency plans to "invest a lot" this year in teaching trial sponsors and EU member state authorities how to use the new system. The EMA is also still working on ironing out the tricky areas of user management and how to transition legacy trials.

Parallel Traders Slam Czech Plan For List Of Non-Exportable Drugs

http://bit.ly/2iPq3IB

European parallel traders are unhappy with a Czech government proposal to draw up a list of "irreplaceable" medicines that are subject to restrictions on re-exportation.

Endo's Opana ER, Generic Oxymorphone Safety Get US FDA Panel Review

http://bit.ly/2jfFnBc

Advisory committee to discuss data on abuse of Opana ER and generic oxymorphone extended-release and immediate-release products.

inside:

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industry should be. His remarks could be viewed a way to push industry into developing solutions on its own to avoid government intervention.

In a research bulletin, Leehrink analyst Seamus Fernadez notes Trump's comments create an environment of uncertainty. As a result, "we continue to recommend that investors focus on companies … that are either in or repositioning their companies toward categories with greater and more durable pricing power, like oncology and rare disease," he said.

Meanwhile, big pharmas are busy positioning themselves as separate from "bad actors" in industry. A number of companies at the J.P. Morgan Healthcare conference emphasized their focus on "transformational innovation" to produce high-value treatments.

TAX REFORM TO STEM EX-US MIGRATION?

Trump's comments also sought to link the drug industry to his narrative about bringing jobs back to the US, which could be read as a

Stock Movements For Top Pharmas* On Jan. 11

COMPANY	CLOSING PRICE JAN. 11	RANGE OF DAILY TRADING ACTIVITY	CLOSING PRICE NOV. 9	CHANGE SINCE NOV. 9
Pfizer Inc. (NYSE)	$32.83 (-1.82%)	$32.40-33.54	$32.12 (+7.07%)	+2.21%
Novartis AG (NYSE)	$72.72 (-1.88%)	$71.86-73.57	$74.29 (+4.22%)	(-2.11%)
Roche (OTC)	$29.48 (-1.70%),	$29.36-29.66	$30.31 (+5.37%)	(-2.74%)
Sanofi (NYSE)	$40.79 (-0.63%),	$40.38-41.16	$42.01 (+4.61%)	(-2.90%)
Merck & Co. Inc. (NYSE)	$61.63 (+2.85%)	$60.75-63.16	$64.18 (+6.07%)	(-3.97%)
Gilead Sciences Inc. (NASDAQ)	$73.77 (-1.65%)	$73.01-$75.55	$78.47 (+5.98%)	(-5.99%)
Johnson & Johnson (NYSE)	$114.73 (-1.23%)	$114.02-$116.25	$120.31 (+2.79%)	(-4.64%)
GlaxoSmithKline PLC (NYSE)	$39.05 (-0.74%)	$38.76-$39.36	$40.40 (+3.22%)	(-3.34%)
AstraZeneca PLC (NYSE)	$28.18 (-1.98%)	$27.97-$28.62	$28.95 (+3.43%)	(-2.66%)
AbbVie Inc. (NYSE)	$61.14 (-3.61%)	$60.59-$63.65	$62.64 (+6.51%)	(-2.39%)
Amgen Inc. (NASDAQ)	$156.62 (-1.35%)	$154.50-$159.16	$146.42 (+5.76%)	(+6.97%)
Teva Pharmaceutical Industries Ltd. (NYSE)	$34.28 (-2.61%)	$33.56-$35.49	$39.97 (+3.10%)	-14.24%
Novo Nordisk AS (NYSE)	$35.62 (-1.08%)	$35.21-$36.03	$34.56 (+2.04%)	+3.07%
Eli Lilly & Co. (NYSE)	$75.26 (-1.32%)	$74.00-$76.92	$78.39 (+5.90%)	-3.99%
Bayer AG (OTC)	$106.96 (+0.18%)	$105.90-$107.22	$102.08 (+3.87%)	+4.78%
Allergan PLC (NYSE)	$216.24 (-2.26%)	$212.05-$222.43	$212.90 (+8.73%)	+1.57%
Takeda Pharmaceutical Co. Ltd. (OTC)	$21.35 (-1.18%)	$21.25-$21.59	$21.35 (-0.37%)	0%
Bristol-Myers Squibb Co. (NYSE)	$56.80 (-5.30%)	$56.53-$58.87	$56.30 (+5.91%)	+0.89%
Boehringer Ingelheim GMBH	NA (private)			
Astellas (OTC)	$14.35 (+0.60%),	$14.28-$14.50	$14.57 (+2.53%)	-1.51%
Mylan NV (NASDAQ)	$37.28 (-4.29%)	$37.08-$39.58	$38.92 (+4.88%)	-4.21%
Biogen Inc. (NASDAQ)	$287.11 (-3.59%)	$285.00-$297.90	$319.86 (+8.21%)	-10.24%
Celgene Corp. (NASDAQ)	$117.24 (-2.28%)	$115.26-$120.81	$120.07 (+10.71%)	-2.36%
Daiichi Sankyo Co. Ltd. (OTC)	$21.58 (-0.44%)	$21.50-$21.65	$21.89 (+0.02%)	-1.42%
Otsuka Pharmaceutical Co. Ltd. (OTC)	$24.74 (+0.73%)	$24.19-$24.78	$21.80 (+1.58%)	+13.49%

*Top 25 companies in Scrip 100 ranking by sales, 2015

willingness to take on corporate tax reform, something the industry strongly supports.

"We've got to get our drug industry back," he said. "Our drug industry has been disastrous. They're leaving [the country] left and right. They supply our drugs, but they don't make them here, to a large extent."

Although he didn't specifically mention tax reform, Trump referred to a situation created by industry's interest in avoiding US taxes, suggesting he might be open to the possibility of a tax holiday, or even broad corporate tax reform.

Even before the press conference, industry has been trying to tie tax reform to US production. Julie Gerberding, executive vice president and chief patient officer in global public policy and public health at Merck & Co. Inc., commented Jan. 10 at the Biotech Showcase meeting in San Francisco that "We manufacture things in places that might not be the most economically efficient over the long run because of the confusion and difficulties that we have with taxes."

Nevertheless, the prospect of tax relief was not enough good news to offset the threat of government price controls. All in all, it was not a good day for industry.

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The Trump Administration: Seven More Things To Watch Out For

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Nobody has a crystal ball to show what life will be like in the biopharma world under the incoming Trump administration, but industry experts were willing to share some personal predictions during panels at the Biotech Showcase meeting in San Francisco, held in parallel with the J.P. Morgan Healthcare conference.

The panels took place on Jan. 10, the day before Donald Trump's market roiling press conference where he advocated bidding for government drug purchases. Trump's call for price negotiations was consistent with his campaign rhetoric but still seemed to catch industry by surprise – another sign that the watchword for his administration will be unpredictability.

Unpredictability is also seen in the Congressional drive to repeal and replace the Affordable Care Act (ACA), which might now become more a reform and rename effort that still leaves the future insurance status of millions of Americans currently served through President Obama's signature piece of legislation hard to predict. But biotech experts have more confidence about other changes like tax reform and a continued push toward greater innovation in the regulation and approval of drugs.

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ACA ... A ROSE BY ANY OTHER NAME

Congress may wind up deciding to have a health system that is just like Obamacare but goes by another name, because the pain of millions losing health insurance may simply be too great if it was repealed, according to Gregory Simon, executive director of the White House Cancer Moonshot Task Force.

The biosimilars approval program was created as part of the ACA and wholesale repeal would mean "it would go down the tubes," Jane Axelrad, principal at Axelrad Solutions and former associate director for policy at the FDA's Center for Drug Evaluation and Research, commented.

But many aspects of the ACA cannot be repealed without 60 votes in the Senate and this will slow the pace of change, Julie Gerberding, executive vice president and chief patient officer in global public policy and public health at Merck & Co. Inc. commented.

Bertram "Norm" Coleman, former Minnesota senator and attorney with Hogan Lovells, noted that change will happen as a vast number of Americans made a choice and elections have consequences. "I do think we will see very significant change and we will see how it plays out," he said.

Speaking at J.P. Morgan, outgoing Centers for Medicare & Medicaid (CMS) Administrator Andy Slavitt spoke out about the danger of repealing ACA without a plan to replace it, and stressed that at the minimum, a new plan must maintain coverage for those currently covered, ensure quality care, bend the cost curve and be fiscally responsible.

TAX REFORM: HOW FAR WILL IT GO?

Biotech Showcase panelists were optimistic about the prospects for tax reform. Companies are holding a lot of cash and would bring it back to the US if there was a tax holiday or if the 35% corporate tax rate was lowered substantially. This might allow an acquisition spree that would stimulate the whole sector.

Gerberding said that she is hopeful for comprehensive tax reform and that resources will come back and be used where they are needed. The current tax laws create unnecessary complexity in biopharma business, she said.

"We manufacture things in places that might not be the most economically efficient over the long run because of the confusion and difficulties that we have with taxes. So hopefully that will be something that will happen and we can all look forward to getting behind," Gerberding said.

Coleman commented in an interview that he thinks there will be tax reform – because there is bipartisan support for it – the only question is how far it will go. Change could come quickly, perhaps in the first 100 days of the new administration, he added.

"There's something magical about the first 100-day period. That is what people will be shooting for," Coleman said.

CONTINUED CHANGE AT FDA

Ex-FDA official Axelrad noted that the new administration is expected to want to spur innovation in the regulation of drugs and that reducing review times will take center stage. However, FDA has already been performing at historically high levels, and the 21st Century Cures Act, which was just signed into law in December, moves it further in this direction.

The new administration may want to push the envelope even further than the new legislation, but it's unclear how far the agency will be willing to go, Axelrad said. If the administration looks to undermine the scientific rigor of the regulatory process, officials will not go along. It may be that the administration will come to appreciate the expertise of FDA officials after they interact with each other, and hopefully conflicts will be minimal, she added.

Merck's Gerberding commented that government was designed for "stability not agility" and that change happens very slowly even when there is demand for it to happen fast. Agencies are very stable and have partners and stakeholders in the real world who are capable of raising red flags when appropriate, she noted.

Axelrad also pointed out that the 21st Century Cures Act gave sweeping new hiring and pay authority to FDA, in response to high unmet need for new staff. In contrast, the Trump administration is expected to apply a government-wide hiring freeze, and it's unclear how that will affect plans at the agency.

BEWARE NATIONAL EMERGENCIES

Overall, Gerberding expressed optimism about the new administration. However, she said that one area she is personally most worried about in the transition period is preparedness for national emergencies – past problems include the flu pandemic, anthrax attacks and Ebola.

New administrations in both parties have a tendency to pull leadership to the center and over-promise, and take control over situations with people who really don't know what they are doing, she said.

> "It would be naïve to think this president wasn't going to have to deal with some sort of bio-preparedness issue — whether its intentional or natural doesn't really matter."
> – Gerberding

"It would be naïve to think this president wasn't going to have to deal with some sort of bio-preparedness issue – whether its intentional or natural doesn't really matter. The apparatus the government needs to pull into action to manage it is complex and requires a fairly sophisticated understanding of how agencies and departments sh ould work together, and it takes a long time to develop that experience," Gerberding observed.

The administration should bring a good person on board to manage this, as lack of preparedness could derail the implementation of new policies, she suggested.

MOONSHOT NO MURDER VICTIM

Simon said he is frequently asked what will become of the Cancer Moonshot initiative, which was spearheaded by Obama's Vice President Joe Biden. The Moonshot exec said that his office expires at the end of the Obama administration unless Trump decides to keep it going.

But Moonshot has "morphed from a program to a movement" and "private sector initiatives will continue regardless of whether there is a PO box in the White House that says 'Cancer Moonshot,'" he said.

"We have provoked an enormous reaction of people wanting to things bigger and faster and better," Simon added.

Funding for the program of $1.8bn over seven years was allocated by a Republican Congress, and it's unlikely that someone will now "come in and kill it," he said. More likely it just will not be led from the White House.

Furthermore, Biden is starting his own cancer initiative as a nonprofit that will continue to convene people around Moonshot, he said. Biden unveiled the new initiative to the biotech community at the J.P. Morgan meeting Jan. 9.

SBIR PROGRAM NEEDS ALLIES

The Small Business Innovation Research (SBIR) program, which provides federal grants for research and development, may not

necessarily be a winner under a Trump regime, panelists said. The basic program was reauthorized through 2022, but many pilot programs are set to expire at the end of the 2017 fiscal year, a National Institutes of Health employee in the Biotech Showcase audience pointed out.

Simon commented that there are "a lot of people who are pro-business who do not want government providing grants like this because they view it as deforming the market, not strengthening the market." Simon advised building support in Congress to keep the programs going.

Former-senator Coleman agreed that recruiting advocates in Congress would be helpful and said that it's sometimes good not to be known too well – as a relatively small program it may fly under the radar.

"You know what happens to a whale that spouts? They harpoon them. So if you have a small program not making a big splash but really making a difference, that is a real asset," he said.

CMS INNOVATION CENTER A POLITICAL FOOTBALL

The CMS Innovation Center is a potential casualty of a Trump administration.

Expert panelists during a session on the CMS noted that the center under the Affordable Care Act has had "enormous discretion to test innovative payment and delivery system models," with seed money to implement new initiatives.

The idea is to experiment with various models with the goal of finding ways to decrease cost, exemplified by the failed proposal to reform Part B payment at the end of the Obama administration.

Mandatory models have proven unpopular with many conservatives, including, notably, Trump's selection for Health & Human Services Secretary Tom Price (R-Ga.), and the center has become a political football, panelists suggested. Consequently, they expect that, at a minimum, mandatory models will be pulled back.

Despite pushback, stakeholders are very supportive of some initiatives and there is bipartisan recognition of the need for value-based payment methodologies, so there may be room for the center to persist in perhaps a different form in the future, panelists said.

"I would hate to see it go away. Republicans were not happy about how much authority it had, but now that the authority rests in their hands maybe they might see it a little bit differently," Liz Fowler, vice president of global health policy at Johnson & Johnson commented.

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FDA

US FDA Headquarters Parking Problem May Create Security Risk

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The US FDA's White Oak headquarters may be at an increased security risk because of traffic and parking problems.

A Government Accountability Office report released Jan. 6 indicates that the agency had yet to implement required security features controlling visitor and employee traffic and by not mitigating known security issues, "may be putting the White Oak campus at risk."

The report reviewed issues related to the consolidation of FDA staff and resources at the White Oak campus, and associated problems that have arisen. Among them was the lack of implementation of some security measures that were required for facilities determined by the government as "high-risk." White Oak obtained the designation because of its physical size, the number of staff, and

Shutterstock: Bork

nature of the laboratories on the campus, according to the report.

White Oak should have a system in place for "controlling vehicle access to and parking on the campus," according to the report. But "in part due to traffic and parking concerns and a desire not to slow the flow of vehicles into parking garages, FDA has not implemented vehicular access controls, such as perimeter vehicular barriers, card access drive-on gates and forced separation of visitor and employee parking," GAO said in the report.

White Oak, a sprawling mix of office, laboratory and other buildings in suburban Maryland, has been FDA's headquarters for about 14 years.

The agency also did not document its reasoning for not implementing the system, according to the report.

White Oak, a sprawling mix of office, laboratory and other buildings in suburban Maryland, has been FDA's headquarters for about 14 years. The agency began occupying the former Naval Ordinance Laboratory in 2003.

The goal was to consolidate employees from multiple locations in the Washington D.C. area into one master campus. Employees moved into the facility in stages, including in 2014 when Office of Generic Drugs and Center for Biologics Evaluation and Research staff occupied the new Life Sciences-Biodefence Laboratory.

SECURITY GATES READY, NOT USED

The campus has had large security gates in place near its entrance for a long time, but they have remained in the open position, allowing all cars to pass.

GAO said in the report that FDA officials indicated the vehicle separation system is functional and awaiting implementation.

It was not used "while awaiting an automation project to be completed around the end of 2016." Agency officials had not documented why its security personnel were not used to implement the vehicle security plan while waiting for the automation project to be finished, according to the report.

GAO recommended that the plan be implemented to ensure White Oak is adequately protected.

FDA concurred and said it planned to implement it in three phases, with full implementation by the end of January:

- **Phase I:** On Nov. 14, 2016, all agency visitors were to be redirected to the North Surface Visitor Parking Lot and would not be eligible to park in employee areas.
- **Phase II:** In mid-November 2016, FDA was to begin testing a "Fast Pass" and security gate traffic light system
- **Phase III:** In mid-December 2016, security gate arms were to be activated and only vehicles with Fast Passes or valid badges will be allowed across the campus security perimeter to park in employee parking areas.

FDA already is short parking spaces for its employees and visitors. Funding limitations kept the agency from building two parking garages that had been included in its campus master plan. GAO said in the report that 51% of parking garage spaces have not been built.

Other buildings that are part of the original master plan also have yet to be built.

OFFICE SHARING CREATES SECURITY PROBLEMS

Much of the problems at White Oak stem from a lack of office space for its staff. As FDA accommodates its growing number of employees, it has created some security concerns.

GAO said that FDA has implemented office sharing and increased use of cubicles to create more space. But that also has led challenges for employees regularly handling "proprietary information related to drug applications or those who handle sensitive personnel related tasks."

A union official representing FDA staff told GAO that "decisions about which staff are assigned to a single versus shared offices are based on various criteria, such as length of time at FDA, but are not based on the sensitivity of the work performed."

GAO's report did not offer any recommendations for changes to employee housing policies.

FDA's space problems are well-known. Some employees have been moved out of the White Oak campus to leased space to create more room for others. And in addition to office sharing, the agency has created desk sharing and hoteling programs, installed cubicles in "common spaces, such as building lobbies," and expanded its telework policy to create more work space, according to the report.

As of April 2016, FDA had nearly 27% more employees than expected assigned to White Oak. There were 10,511 people the agency had to accommodate on the campus, as opposed to an expected 8,297, according to the report.

FDA Commissioner Robert Califf has said the existing campus is out of space. The agency already is working on a new plan to determine its needs both at White Oak and nearby.

But there does not seem to be much support in Congress to add buildings. In an FY 2017 Senate appropriations bill, Congress told the agency that it should explore innovative funding options and partnership opportunities to meet its space needs.

FDA also blamed space management problems in part on Obama Administration directives to freeze and shrink the federal building footprint.

And ironically, as the agency has reduced the amount of space it leases, it has cost more for it to occupy the new space at White Oak.

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Post-Brexit UK Could Be 'Back Of The Queue' For Drug Access, Warns MHRA Chair

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As UK prime minister Theresa May prepares to trigger Article 50 sometime within the next three months, the chair of one of the UK bodies that will be most affected by Brexit – the Medicines and Healthcare products Regulatory Agency – has expressed concern that the country could be relegated to the "back of the queue" in terms of access to new drugs.

MHRA chair Professor Sir Michael Rawlins also raised concerns over the loss of revenue from the work that the MHRA currently does on behalf of the European Medicines Agency, and the possibility that international companies might be tempted to move their headquarters and follow the EMA if it relocates to another country in Europe.

Giving evidence before the House of Lords science and technology select committee on Jan. 10, Rawlins said that whatever the future arrangements between the UK and the EU, his agency would continue to ensure all medicines marketed in the UK were of high quality, effective and safe.

But as a non-member of the EU, and with the MHRA no longer an integral part of the EU regulatory network, he feared that the UK could become a much less attractive proposition for companies seeking early launches in key markets.

"One of the biggest worries I have about Brexit and standing alone as a regulator is that we are only 3% of the world market for new drugs, and if we're not careful we're going to be at the back of the queue." Japan, the US and the EU would be at the front, he said.

This is not the first time the specter of delays in new drug approvals and launches following Brexit has been raised, but it is significant that the chair of the MHRA, a highly regarded medicines agency and a key contributor to the work of the EMA and the EU regulatory network, sees it as a real possibility.

Rawlins told the committee it was important to "put ourselves in the position where we can be in the front of the queue, not in the back." One way of doing this, he said, would be to speed up access to new drugs by ensuring that the MHRA's regulatory evaluations and the health technology assessments conducted by the National Institute for Health and Care Excellence (NICE) were carried out in parallel, not sequentially.

Noting that the UK Early Access to Medicines Scheme already allows drugs to be made available on the National Health Service before marketing authorization where there is a clear unmet need, Rawlins also raised the possibility of the UK issuing conditional drug approvals – something that the EU already does for certain centrally authorized products.

He suggested that the MHRA could in fact become "swifter than the EU" in terms of the overall approval process. "In the end it is not the EMA that gives the marketing authorization, it's the [European] Commission… and they take on average 67 days. As someone I know very well in the pharmaceutical industry said, each day of delay for a pharmaceutical marketing authorization costs a company about a million dollars, so that's 67 million dollars gone just waiting for the commission to decide to meet *en collège*. That's just one bit of it and there are many other aspects. Without impeding the quality or the standards or anything like that, we would want to speed up the process."

THE EMA AND THE FUTURE RELATIONSHIP

A key question is whether, and if so how, the UK might continue to play some sort of part in the EMA and medicines agency regulatory network post-Brexit, especially if the EMA moves elsewhere – the MHRA does "about a third of the scientific reviews" for EU new drug applications, Rawlins said.

Asked whether the EMA would relocate, he said that "allegedly it is not legally obliged to move but it seems politically difficult for the European Commission to have one of its significant agencies outside the EU, so I presume it will go."

This, he said, would be "a great loss for a number of reasons: it is 20 minutes on the tube to our offices in Victoria, and one of the reasons why international companies have their base in the UK is to be close to the regulator. Japanese companies for example are based in London or the southeast of England, and that is a great worry – will they move to wherever their regulator goes?"

If the EMA does relocate, and the MHRA becomes a more "standalone" agency, its workload could increase and it would also lose a sizeable chunk of its income. One member of the committee asked whether the agency had discussed how to resource any extra work it had to take on, and suggested it might have to "staff up colossally".

Rawlins said the extent to which the UK remained part of the EU regulatory framework would determine whether it needed to take on more staff and resources. "If we are part of the system, no we wouldn't, but as a sovereign regulator, yes we would have to.

We have been discussing it for some months now with ministers and officials in the Department of Health, pointing out some of the intricacies of it all."

One issue, he said, was the fee waiver offered to companies seeking approval of an orphan drug, which is currently covered by the commission. "Now, what are we going to do with that? There will have to be a cost somewhere along the line, otherwise we might lose orphan drugs, which would be a tragedy."

Moreover, he pointed out, unless the MHRA could "come to some arrangement" with the EU, the MHRA would no longer do the detailed assessment work that it currently does, "which we get paid for. We get money when we do the detailed scientific assessments, and that would go."

He said there were "two broad options" for the UK post-Brexit. One was to "remain within the system" and contribute to scientific discussions in the regulatory network. "We might even be able to remain within the system not just operationally but also have influence over new regulations and directives."

If, on the other hand, the MHRA became a "sovereign regulator" it would need some kind of mutual recognition arrangements with the EU, for example in inspection activity. "We contribute to the EU inspectorate, going round India, China, looking at manufacturing sites, but we can't do that on our own. We need to share the burden."

As for new drug approvals, he dismissed a suggestion by the committee that the UK could simply accept decisions taken by another regulator – the US Food and Drug Administration, for example. "It has been suggested that we just rubber-stamp decisions made elsewhere," he noted. "I would regret that for all sorts of reasons." Such a move, he said would "emasculate the MHRA and the UK would not have a strong regulator."

POTENTIAL BENEFITS

Also facing the committee's scrutiny was Dr Beth Thompson, senior policy adviser at the Wellcome Trust, who focused on issues such as the regulations governing clinical trials, data privacy and the use of animals in research, and the fact that the UK and EU rules are closely entwined with a "variety of different models of regulation and enforcement."

She said that continued equivalence or harmonization would be "a benefit and there are some elements of that you would want to keep," citing the EU clinical trial portal provided for in the new Clinical Trial Regulation that will allow data to be shared among regulators.

"If you are in the UK setting up a clinical trial and you need a bigger population, for example you want to cover the EU countries too, this will make it easier to do so – there will be real benefits for countries setting up multi-country trials, also for rare diseases, to be part of a harmonized approach."

But Thompson also pointed out some potential upsides to Brexit, noting there were areas where the UK could be more flexible and introduce more "risk-proportionate" regulation, for example in gene editing and data privacy.

"There is real potential that we could use the UK almost as a test bed to try out new regulatory approaches and within a robust framework be more experimental. We have seen with mitochondria donation that the UK regulators are in a really good place to try some very innovative things, and that will bring new treatments to patients faster and make the UK a great location to do research," she said.

Published online January 10, 2017

FDA's NDA And BLA Approvals: Arymo ER

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				
Egalet	*Arymo ER* (morphine sulfate)	Extended-release formulation of the opioid for long-term pain management, with abuse deterrence claim for intravenous use	*S, 5*	*1/9/2017*
Matheson Tri-Gas	Nitrous oxide			192017

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

Oncology In 21st Century Cures: Heading Toward A Two-FDA Solution?

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The 21st Century Cures Act includes a lot of FDA-related reform provisions, but it is not a transformative piece of legislation for the US agency.

The bipartisan encomiums about a new era of innovation and the howls of complaint about lowering standards from a handful of dissenters notwithstanding, there is nothing in the Cures law that will have an immediate impact on drug development. And, in a climate where FDA is generally getting high marks for supporting innovation, that is probably as it should be.

But the new law, signed by President Obama Dec. 13, could yet be remembered as the start of something big: the inauguration of an era where FDA's cancer review activities are further elevated into a separate sphere of activity from all other medical product regulation.

No, there isn't any immediate path to a separate "Cancer FDA." But the pieces are in place for FDA to evolve so that cancer products have a more formal, independent status. Think about the National Cancer Institute within the National Institutes of Health, where the NCI director is independently confirmed by the Senate and many activities have dedicated authorization and funding.

FOLLOW THE MONEY

There is no provision of Cures that talks directly about that idea. But that may still be the implication of the patchwork of changes put in place.

The trick, in the classic Washington approach, is to follow the money. The Cures law dedicates $20 million in new funds to FDA in 2017 – and, unlike the remaining $480m promised to the agency over the next nine years, that is actually appropriated to the agency. And of that amount, $15 million is dedicated to the launch of the Oncology Center of Excellence.

The law itself simply directs FDA to create one inter-center institute; the agency is already well underway in setting up OCE, under the direction of the Office of Oncology & Hematology Products Director Richard Pazdur.

The plan, for now, is to have Pazdur oversee clinical reviews for all oncology therapies, regardless of whether they are therapeutics, biologics (cell, gene or tissue-based therapies), devices or diagnostics. The underlying application will still go to the traditional center, which will retain sign-off authority and conduct all the non-clinical aspects of the review.

FDA can, if it chooses, create more than one Inter-Center Institute, though as outgoing FDA Commissioner Robert Califf noted during the Prevision Policy/Friends of Cancer Research Biopharma Congress in November, there is no practical way to create a dedicated center for every disease. That strongly suggests OCE will be a unique structure within FDA.

The new funding in Cures will help ensure that the oncology center is not strictly "virtual" – it will actually have dedicated resources, at least in the initial phase. Putting it in statute makes a difference, too.

The statute authorizing the Inter-Center Institutes explicitly directs the new group to "streamlin[e], where appropriate, the review of medical products to diagnose, cure, mitigate, treat, or prevent the specific diseases relevant to the major disease area of focus of the Institute, applying relevant standards under sections 505, 510(k), 513(f)(2), and 515 of this Act and section 351 of the Public Health Service Act, and other applicable authorities." It also stipulates that the new institute will develop "strategies to recruit, train, and provide continuing education opportunities for the personnel" involved, and also to enhance "the interactions of the Centers with patients, sponsors, and the external biomedical community."

That language could be read as encouraging the new OCE to apply best practices for any group in FDA. However, it is also a legislative justification for housing the most cutting-edge practices within OCE – the new group may literally not be bound by procedures for any other type of product review. (The relevant statutes still apply, of course – but not necessarily the policies and procedures.)

LITTLE CHANGES COULD ADD UP TO BIG IMPACT

Moreover, many of the other "little" changes in Cures might be much bigger in the context of oncology. For the most part, the changes in areas like streamlined supplemental NDA approvals, real-world evidence, innovative trial design and "platform" approvals are permissive rather than prescriptive: FDA is authorized to do a lot of different things, but not required to apply the new tools.

But all of those changes are in areas where the oncology team is already taking the lead. The oncology group pushed for the chance to review supplemental NDAs using data summaries, for example, and the group has also taken the lead on pilot projects to apply real world evidence for efficacy purposes. And the oncology group has also been the leader in pushing for hyper-fast reviews and also on delivering high numbers of approvals.

With the pipeline still full – FDA estimates that between a third and 40% of NMEs in development are for oncology indications – there is a strong case for the oncology group to continue to innovate on regulatory approaches.

The new law also allows FDA to terminate the institute once it is established – but requires 60 days advance public notice that includes a rationale for abandoning the project. That is an important difference between having OCE in statute rather than created by agency action alone: it won't be up to FDA to decide on its own whether a separate cancer review model is worth keeping.

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

New European Monographs Set 'Robust Standards' For Biosimilar Development

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A pilot study on biotherapeutic monographs just completed by the European Pharmacopoeia has shown that "robust" public quality standards can be established for complex molecules and used in the development of biosimilars as more biological drugs come off patent.

The European Pharmacopoeia (PhEur) said that monographs have already been published for many first-generation biotherapeutics, including peptide hormones and interferons, but that other substances, such as interleukins, coagulation factors and monoclonal antibodies, have recently faced or will soon be facing patent expiry. There is therefore a need to ensure that when a patent for one of these more complex biotherapeutic products runs out, "a public standard for future products is already in place," it said.

To address this question, the pilot was launched in 2008, starting with insulin glargine and the human coagulation factors. It was enlarged in 2011 to cover more diverse classes of approved biologic drugs, including hormones, fusion proteins, pegylated products and hyperglycosylated proteins. "This saw the addition of teriparatide, etanercept, pegfilgrastim and darbepoetin alfa to the PhEur monograph elaboration process," according to a scientific paper published by the PhEur.

Four new monographs have been adopted and published under the pilot, for insulin glargine, rDNA Factor VIIa, rDNAFactor IX, and teriparatide. A fifth monograph, on etanercept, was adopted in November last year, rounding off the pilot.

According to the paper, the pilot phase "successfully proved that it is possible and extremely useful to elaborate monographs on complex biotherapeutics; in the specific case of etanercept, the monograph elaboration showed that complex molecules and complicated assays can be standardised."

Four new monographs have been adopted and published under the pilot, for insulin glargine, rDNA Factor VIIa, rDNAFactor IX, and teriparatide. A fifth, on etanercept, was adopted in November last year.

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THE PROCEDURE

The pilot was conducted using the P4 procedure, which is usually applied to chemical products still under patent where a single manufacturer has been identified and there is potential for future generic production, and involves close collaboration with the originator company. As it involves biotherapeutics, the pilot has been dubbed P4Bio.

The scientific paper noted that biotherapeutics require more flexible monographs than chemical substances, and that a key challenge has been how to translate this flexibility into a public standard that provides sufficiently prescriptive quality requirements and allows for the development of biosimilars.

The pilot has established the first monographs which allow for the control of the quality of new single-source biotherapeutics while recognizing their inherent complexity, the paper said. "The monographs for these biotherapeutics also firmly establish the link between product quality and production process. These monographs have allowed for flexibility in the approach to setting specifications by typically including complex tests that measure process-dependent microheterogeneity (e.g., glycosylation) in the Production section of the monograph."

Describing the P4Bio pilot as "a success story and another positive example of the advantages of close collaboration across the scientific community," the PhEur said it had decided to transform the pilot phase working party into a formal group of experts.

Pharmacopoeial monographs can be used by manufacturers, regulatory bodies and other stakeholders to ensure the quality control of active pharmaceutical ingredients and finished products against internationally recommended specifications. The PhEur warned recently that regulators in some countries with "less stringent regulations" were using compliance with the monograph, rather than a formal comparability exercise, as a demonstration of biosimilarity.

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Reign In Your Distributors And Reps, Chinese Regulator Cautions

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At its first press briefing for 2017, China's National Health and Family Planning Commission (NHFPC) said it is preparing to roll out nationwide a new receipting system for pharmaceutical trade designed to improve transparency and control the current multiple layers of price markups inside the distribution system.

The official guidance for the scheme was released on Jan. 9. "The goal of this reform is to tackle drug price inflation," noted Liang Wannian, deputy director of the China Health Reform Office and the director of NHFPC's Medical Reform Bureau, during a press briefing the same day.

"Our task is to squeeze the inflated portion out of pharma distribution channels and use the savings to raise compensation to physicians. Such measures of 'emptying the cage for new birds' are what we always promote."

TWO RECEIPTS

The new *Liangpiao* (two receipts) scheme requires hospitals to inspect two sets of receipts for all drugs that they purchase before accepting them – one issued by drug manufactures and the other by distributors.

Starting from public hospitals in selected health care reform pilot cities, the new requirement asks distributors to issue formal *fapiao* (receipts) to hospitals, and distributors meanwhile should present hospitals with receipts issued by drug manufacturers.

There are several exceptions to the rule, including for foreign drug firms' national domestic distributors and holding companies' subsidiaries, which will both be considered to be manufacturers under the receipts system.

MAJOR IMPACT?

Given public hospitals' absolute dominance over drug tenders in China, the national rollout of the Liangpiao system is expected to drastically shake out smaller distributors and accelerate consolidation in the sector, and the impact on manufacturers could also be significant given the current opaque nature of the receipting system.

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The national rollout of the Liangpiao system is expected to drastically shake out smaller distributors and accelerate consolidation in the sector.

The frontrunner in the implementation push will be Sanming in Fujian province. The city started a major health care reform process in 2012, requiring hospitals to check the two receipts to ensure minimum inflation of end drug prices.

The changes have cut down the number of distributors from over 200 to 62, while distribution costs have been reduced by 2-3%.

'COMMERCIAL MISBEHAVIOR'

Despite the seeming official emphasis on pharma distribution, the director of Sanming City's Drug Reimbursement Office, Zhang Xuanhua, also cautioned drug manufacturers about new types of commercial misbehavior under the revised system. "Drug price inflation has become an eyesore laden with layers of interests," Zhang observed.

"It has affected upstream drug manufacturers, and [distributors] manage to control makers using established sales networks," Zhang said during a briefing. "Medical sales in the past used to use tactics such as overcharging and money laundering when there existed layers of distributors, and national distributors sold drugs using a base price [with multiple layers of markup]."

But the official explained that there are now some new tactics. "Because under the Liangpiao system they can't do the same, medical sales firms now have drug makers issue receipts with inflated drug prices, then through advertising agencies and conference companies, which they set up to provide fake receipts, 'launder' money from the makers," Zhang emphasized.

NEW EVIDENCE

At the start of the New Year, China's state broadcaster CCTV aired a report in which an undercover reporter went to hospitals in Shanghai and Hunan, and unearthed cases of sales reps handing over envelopes of kickback money to working physicians, based on the amount of sales they prescribed.

The footage stirred up a firestorm, stoking renewed fears that another official bribery crackdown is imminent following the one in late 2013 when GlaxoSmithKline PLC found itself at the epicenter of a broad compliance crackdown.

Sanming's Zhang meanwhile had some stern words for medical sales staff. "Medical sales is a legal occupation and serves to promote drug products. But now, some sales reps serve selling products, which is a change in nature [of the profession]," he told the press.

"Medical sales using kickbacks, cash and gifts to bribe medical facilities, physicians and medical insurance management personnel in exchange for product sales, as well as breaching supply orders without legitimate reasons, will be blacklisted," Zhang warned.

From the editors of PharmAsia News. Published online January 10, 2017

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How To Audit Contract Manufacturers For Data Integrity Breaches

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When auditing contract manufacturing organizations (CMOs) for data integrity problems, the pharmaceutical industry should pay careful attention to the analytical laboratory, because this is where many of the lapses are found by FDA investigators.

So asserted Patricia Frech-Baur of Amgen Inc., who touched on some of the specific data integrity problems she observed in auditing CMOs at the Parenteral Drug Association's recent Outsourcing CMO Conference held in Washington. DC. She also gave some advice on how to decide which contract manufacturers to audit first. Frech-Baur is the senior manager of quality operations of Amgen in Switzerland.

Frech-Baur said that one general observation she had about auditing sites is inadequate review of electronic audit trails to ensure that all data is captured and not deleted or replaced. "When we asked why are you not doing audit trail reviews, they all say they have not gotten to it yet. They say they are focusing first on QC; this is fine. Nevertheless, the inspector will not stop at QC, they will come into the production lab to see how you have control over your data."

Frech-Baur said that FDA's relentless focus on data integrity issues is not going away anytime soon. This focus is driven by increasing sophistication among the agency's investigators on knowing what to look for in electronic systems during inspections. There is also the perception that CMOs know less than manufacturers and have less experience in data integrity.

She said that "[FDA] is coming back to us and pressure testing us, the manufacturer as well and the CMO. Do we really know what we're doing and do we know how to handle raw data?"

Data integrity failings continue to be a common problem found in drug GMP warning letters. Seven of the nine drug GMP warning letters issued to finished drug and API manufacturers in the first five months of this year raised data integrity concerns, surpassing the six data integrity warning letters that FDA issued in the first five months of 2015.

Frech-Baur noted that regardless of whether drugs are produced internally or by external partners, the drug product owner is ultimately responsible for the product and needs to demonstrate control over the data.

Frech-Baur noted that regardless of whether drugs are produced internally or by external partners, the drug product owner is ultimately responsible for the product and needs to demonstrate control over the data.

She cited recent data showing that the majority of data integrity problems, 62%, emanate from inadequate handling of electronic records in laboratory systems. Another 24% were from inadequate quality oversight, and 10% came from inadequate production systems. This data was presented by consultant Ronald Tetzlaff of Parexel International Corp. at a PDA meeting in September.

The data tracked trends from 66 warning letters FDA sent to manufacturers in 18 countries for data integrity violations over a four-year period, from 2012 to 2016. Most of the warning letters were sent to sites in India and China. India received 30 warning letters during this period and China received 12.

This information prompted Amgen to target its data integrity audits on the laboratory.

A recent review of drug GMP warning letters by the former Gold Sheet also showed a similar pattern of FDA focusing on data integrity problems in the analytical lab. FDA sent 15 warning letters to drug manufacturers and CMOs for high performance liquid chromatography (HPLC) related data integrity problems over a five-year period, from 2010 to 2014.

Amgen's data integrity audits revealed the following shortcomings at CMOs:

- **Unclear procedures for conducting peak integration of chromatograms.** Frech-Baur said that "most QC labs have automatic integration [of chromatograms], this is fine. Yet sometimes peaks need to be manually integrated because of baseline considerations." In this case, the CMO did not have procedures for how to manually set the curves in chromatograms. "This was not well defined so it was left to other people to decide where to set the curves. This is definitely a data integrity issue that can lead to an observation."
- **No raw data records for "simple systems" such as pH, balance and thermometers.** Frech-Baur said that at one CMO, a QC operator interviewed stated that simple systems such as pH meters and balances were not connected to a printer and that their values were written directly into the logbook without verification. This was a no-no. She said that not storing raw data from these systems makes it too easy to falsify information. "If you make your pH a 12 and you see that the data is not right you can measure it again and test this into compliance or you can change the number. This is easy to do. This is what the regulator will look at. They want to see compete control." She said that such systems can in fact be connected to a small printer. Without this raw data it is possible to manipulate data or repeat testing to achieve a desired outcome with limited opportunity for detection.
- **The printed HPLC copies were used as raw data and the electronic data were deleted.** A QC operator interviewed during the assessment stated that the printed paper copy of the HPLC chromatogram is considered a true copy, hence they defined it as raw data as required by 21 CFR 211.180(d) and deleted the electronic files. Amgen said that printed paper copies from complex systems are not considered true copies of the entire electronic raw data since they do not include the injection sequence, instrument method and integration method used to create the chromatogram. Frech-Baur pointed out that only print-outs of static records such as pH meters or weight measurement can be considered raw data or a true copy.
- **Turning on and turning off audit trails.** She said that in one audit an operator admitted to turning off audit trails to configure the system or to delete sequences of non-executed runs. This was the wrong thing to do, said Frech-Baur. The observation was that system should be configured in such a way that nobody should be able to turn off or on the audit trail. It was also observed that all users had a common ID password. Each user needs in individual password.
- **No computer validation at the user site.** Frech-Baur stressed that CMOs must validate computer systems, and it is not enough to rely on the pharmaceutical manufacturer to conduct such validation. She said that a user interviewed during the assessment was asked if the computer software had been validated to assure that it performs for its intended use. The user said that the software was validated and provided a copy of the letter received from the vendor indicating that the software was validated. This was not sufficient, said Frech-Baur. The CMO should be validating the computer software on its own.
- **Electronic audit trails not reviewed.** Operators interviewed during the assessment confirmed that they did not review audit trails of batch records to determine if unapproved changes had been made. The observation was that there were no procedures in place to conduct audit trail reviews of critical data or complex systems.

CLICK

We have an online page focused on the manufacturing issues.

FIND IT AT: https://pink.pharmamedtechbi.com/manufacturing

Frech-Baur said that during audits "we set up clear expectations, and if we come in and find a deficiency we expect that it will be fixed."

She said that the end goal of doing these audits is ensuring that "all of our CMOs are in compliance with data integrity."

Amgen developed a risk-based selection model to help guide decisions on who to audit first since there are so many partners involved in manufacturing drug products as well as contract labs involved in release testing.

Frech-Baur said that high-risk sites are inspected before low-risk sites. CMO sites that make high-revenue or high-demand drugs are considered high risk. Sites for medium-demand drugs are medium risk; sites that manufacture low-demand drugs, that package drugs or that make starting materials are considered low-risk sites.

Analytical testing sites are deemed high risk if they test clinical or commercial drug substances or drug products; medium risk if they test packaging components or cell banks or do import testing; and low risk if they test raw materials.

Amgen does not conduct data integrity audits of low-risk sites and instead requires written confirmation that verifies that the CMO or testing lab has a data integrity policy in place as well as a training program in place for employees.

Frech-Baur also advised that it is important to stress that the audit is more of a partnership effort between the manufacturer and the CMO. "It is really advisable to conduct a data integrity assessment as a collaboration and not just going in as an audit. You get so much more out of it when you have a strong relationship with your CMO."

From the editors of Gold Sheet. Published online January 6, 2017

Why Excipient Suppliers Should Dump Most DMFs Prior To May Deadline

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Excipient suppliers need to decide soon whether to convert their paper drug master files (DMFs) for existing drugs to electronic form or to inactivate them and consider alternative approaches for handling proprietary information. One such alternative would be to provide this information directly to manufacturers instead of FDA under confidential disclosure agreements.

So asserts a position paper just issued by the International Pharmaceutical Excipients Council. The paper outlines some of the challenges involved in converting paper DMFs to electronic files and offers some alternatives to the traditional DMF for disclosing proprietary information.

In May 2015 FDA published final guidance that established a deadline of May 5, 2017, for DMFs to be submitted in the electronic Common Technical Document format. The new requirement only applies to submissions going forward; there is no requirement to resubmit anything that has already been submitted in paper. A DMF is a submission of information to the US FDA to permit the agency to review information on a drug component in support of a third party's drug application. The primary purpose for establishing a DMF is to maintain confidentiality of proprietary information.

IPEC said that while there is no requirement to convert existing paper DMFs into the eCTD format, it is "realistically impossible long-term for excipient suppliers to maintain paper DMFs since all future updates, amendments, annual reports and letters of authorization (LOAs) will be required to comply with eCTD format and electronic submission specifications (including XML backbone and submission through an approved FDA portal)." An LOA grants FDA the authorization to review the DMF.

There is also concern that drug product manufacturers may expect their suppliers to have eCTD compliant DMFs by May 2017.

The group also said that "many excipient suppliers do not have the software required for eCTD publishing, nor do they have systems that can communicate directly with the FDA computer system; therefore updating excipient DMFs to eCTD format would require significant resources that would need to be justified."

To ensure their optimal use, DMFs should be used in the following situations:

- Excipient suppliers should only submit or maintain a DMF if they have confidential information on non-compendial, co-processed or novel excipients that they do not want to share directly with the customer.
- A DMF may also be submitted for a compendial excipient where proprietary toxicology information is necessary to support new routes of administration or higher levels of use than what was previously approved and the DMF holder chooses not to share the information directly with manufacturers.

IPEC suggested that DMFs be inactivated for compendial excipients and some types of non-compendial excipients such as simple mixtures of common excipients since they "often do not provide added value to regulators."

David Schoneker, global regulatory affairs director for Colorcon, and a past president of IPEC, told the Pink Sheet that "a pretty high number" of excipient manufacturers use DMFs for communicating proprietary information, yet some also use confidentiality agreements with pharmaceutical manufacturers.

He further noted that the content of DMFs varies: while some may only be a few pages, others may be thousands of pages long. Some DMFs include full toxicology reports or quantitative formulations which can make them very large or they might only include a basic description of a key manufacturing step that is considered highly confidential.

He said that "there is no standard historically for the formatting, which is why it would be very difficult for many of the old DMFs to simply be converted into the eDMF format, which requires the information to be in CTD format. Most excipient DMFs have been around for years and are not in CTD format and many excipient companies have limited desire to do much work to convert the files since they only sell small amounts into the pharmaceutical industry."

Excipient manufacturers should decide before May 5, 2017, whether to close or inactivate existing DMFs or convert them to an eDMF in the eCTD format.

From the editors of Gold Sheet.
Published online January 11, 2017

ANDA Stress Test: End-Of-Year Submission Bolus Pressures US FDA Review System

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FDA's generic drug workload increased substantially in December and may provide a stress test of sorts for its enhanced review system and approval pace.

Sponsors submitted 235 abbreviated new drug applications in December, the most received in a single month since the famous June 2014 avalanche when 635 ANDAs arrived. While sponsors tend to push more applications in December than normal to close out their calendar years, the 2016 number is unusually high. In December 2013, there were 225 ANDAs submitted, but throughout the generic drug user fee program era, no other December rush has approached the 2016 total (*see box*).

Industry now has submitted 424 ANDAs through the first quarter of fiscal year 2017 and is on pace to send nearly 1,700 ANDAs for the entire fiscal year. That total would break the GDUFA record for annual submissions set in FY 2014 (the year of the avalanche) when FDA received 1,473 submissions (*see charts, p. 18*).

The growing total likely will increase the pressure on FDA's ANDA review staff to meet its GDUFA goals, in addition to gain better control of its workload. Under the generic user fee program, nearly all of these new submissions, 90%, are scheduled to receive a first action (which can be an approval, tentative approval, refuse-to-receive, or complete response) within 10 months.

The growing total likely will increase the pressure on FDA's ANDA review staff to meet its GDUFA goals, in addition to gaining better control of its workload.

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DECEMBER MONTHLY ANDA SUBMISSION TOTALS

- **2012:** 163
- **2013:** 225
- **2014:** 43
- **2015:** 180
- **2016:** 235

The 10-month clock is the most aggressive review goal of GDUFA so far. As more sponsors look to take advantage, the agency may have a tougher time moving the applications through its systems within the required time. The Office of Generic Drugs wants to maintain its workload at a steady state, but it does not appear it has reached it yet.

OGD also does not want the applications under review confused with the official GDUFA backlog, however. Agency officials have argued that a number of applications remain pending because industry has yet to respond to FDA questions or requests.

This latest bolus also may spark concerns that FDA once again will be sending more refuse-to-receive or complete response actions in the coming months because a number of applications are incomplete or otherwise not approvable. After a bolus in December 2015, the agency refused a substantial proportion of the applications.

However, there seem to be some signs that application quality may be improving. The agency has seen its refuse-to-receive actions decrease significantly in FY 2017, suggesting that more ANDAs may include all the necessary information.

WHY ALL THE ANDAS NOW?

Ultimately, it may be hard to define a specific cause of this ANDA rush. The FY 2014 avalanche was triggered in part by sponsors' efforts to avoid enhanced stability requirements that were set to go into effect.

When the FY 2017 submission wave began, it was suspected that sponsors were most interested in the 10-month review clock, which was five months faster than the 15-month clock promised the previous fiscal year.

FDA told the Pink Sheet that it is committed to meeting its obligations under GDUFA, "but we cannot speculate about apparent short-term submission trends and what effect those may have on the review process."

Brian Malkin, senior counsel at McGuireWoods, said a reason for the rush is difficult to determine because there are a lot of unknowns about what changes will be made

by President-elect Trump and the renewed generic drug user fee program.

Trump has promised to shake up the federal bureaucracy, including FDA. A few names have been floated for FDA commissioner, who may have different views than Robert Califf, who is expected to depart in the coming days.

Further on in 2017, FDA might see another end of fiscal year slowdown and then surge in October, since GDUFA II is slated to make several changes, including creating a priority review pathway and allowing pre-submission meetings for complex product sponsors.

APPROVAL PACE REMAINS ROBUST

Despite the submission bolus, the agency continued its elevated approval pace.

FDA posted 56 full approvals in December, which is in line with the average for the first two months of the fiscal year. The agency now has cleared 169 ANDAs through three months and is on pace to notch 676 for the full fiscal year.

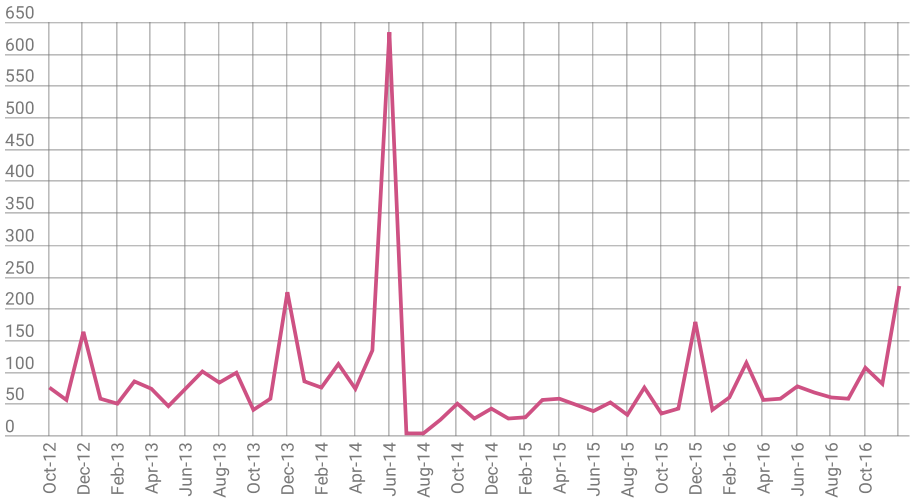
It would surpass the record total of 651 set in FY 2016.

The agency also has issued 47 tentative approvals through the first quarter of FY 2017, or 15.7 per month, which is slightly ahead of its FY 2016 pace of 15.3 per month.

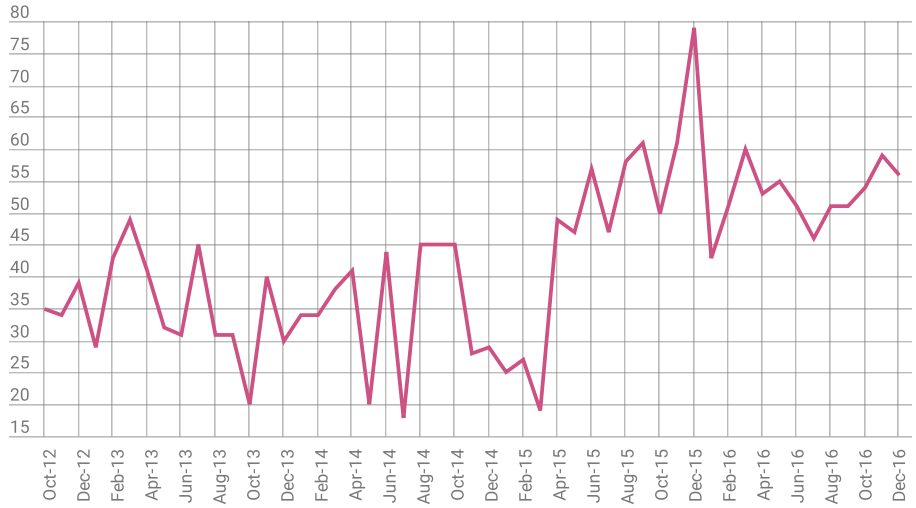
Elevated approval levels could generate some attention going forward as the drug pricing debate continues. Congress and other stakeholders have been pushing FDA to approve generics faster to add pricing pressure.

Published online January 9, 2017

ANDA Submissions Balloon In FY 2017...



But Approvals Still Holding Steady



In December, sponsors submitted the second highest number of ANDAs in a single month during the GDUFA era and are on pace to submit a record number for all of FY 2017. Approvals dropped slightly during the month, but remained in line with their current pace.

Source: FDA Generic Drug Program activity report data

CHPA Optimistic Voluntary Drug Takeback Efforts Will Stall Spread Of Mandates

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The Consumer Healthcare Products Association points to the results of its work with two counties on educating consumers on drug disposal to counter the momentum from nearly a dozen local governments and one state requiring the drug industry to foot the bill for takeback programs.

CHPA President Scott Melville

"County-by-county mandates are not efficient, are incredibly costly and difficult for manufactures to comply with," said CHPA President and CEO Scott Melville. "And it's not what we are in business to do. We are in business to innovate, to bring medicines to people, to keep costs down."

CHPA, along with partners from the pharmaceutical industry including the Pharmaceutical Research and Manufacturers of America, believe consumer education through online and grassroots campaigns are most effective to resolve concerns about disposal. In Los Angeles County, Calif., and Cook County, Ill., the industry groups already are working with municipalities to publish information on proper disposal of medication and where to find disposal bins in those counties.

CHPA made fighting the spread of local, mandated drug collection programs as one of its top priorities in 2016.

The trade group also is committed to fighting against state bills, though Melville suggests a state-wide requirement is better than a patchwork of varying regulations in different counties. Massachusetts in 2016 became the first state to mandate a drug disposal program as part of broader legislation on curbing distribution of opioid and other frequently abused drugs.

County mandates have passed in recent years, are in various stages of implementation in several states and will be considered in some state legislatures. California accounts for the majority, with ordinances passed in Alameda, Contra Costa, Marin, Santa Barbara, Santa Clara, Santa Cruz, San Francisco and San Mateo counties. King and Snohomish counties in Washington have also passed ordinances.

The ordinances are intended to combat what local officials and state legislators, prompted by human health and environmental activists, see as a threat of contamination in waterways, as many consumers flush products. Industry estimates place the amount of leftover drugs thrown in the trash, flushed or stored in medicine cabinets in the US at around $1bn annually.

CONSUMERS UNAWARE OF FLUSHING RISKS

FDA, the Environmental Protection Agency and Drug Enforcement Agency all say disposal in household trash is the best approach, except for controlled substances that are at risk for abuse and should be flushed, Melville said. However, consumers typically are not aware of the risks of flushing products or of voluntary receptacles for collection already in their areas.

In a national disposal survey conducted in 2015, CHPA found consumers generally want to dispose of their medicines in the right way, but most are not sure how and 62% had not looked into the issue.

The survey showed knowledge of existing takeback bins is the problem, but should not be tackled by mandatory industry-funded takeback programs, according to CHPA.

Additionally, local mandates will impact the price of products, Melville suggested. "These mandates add to the cost of medicine, make no mistake about it, particularly when you are talking about low-cost or low-margin products like OTC medicines and generic drugs," he said during an interview.

Melville added that existing ordinances already are costing the Rx and OTC drug industries "tens of millions" of dollars. "Takeback programs are expensive responses to unsubstantiated problems and they don't even solve the problem they're trying to solve," he said.

PhRMA estimated that the Alameda County program, which serves a population of around 1.6m, costs about $1.2m annually.

Each program includes multiple elements. For example, in the King County program launched in September 2016, industry is responsible for funding most costs associated with 77 secure dropbox sites, including at 38 retail pharmacies, 22 hospitals/clinics and 17 law enforcement centers, according to data from Community Environmental Health Strategies LLC, a Washington state organization that helps government agencies, businesses and other entities develop and implement environmental health strategies.

Industry challenged the King County ordinance in a 2013 lawsuit, arguing it violated the US Constitution Commerce Clause prohibiting local or state regulatory interference with interstate commerce. The lawsuit was put on hold to await the outcome of similar legislation by the Rx industry fighting the Alameda County ordinance, which affects only Rx drugs.

The King County litigation stalled when the US Court of Appeals for the Ninth Circuit in 2014 found the Alameda program "neither discriminates against nor directly regulates interstate commerce." CHPA joined PhRMA in appealing to the Supreme Court, however the high court refused the case.

LA, COOK COUNTIES PROVIDE MODELS

The industry's work with Los Angeles County and Cook County are examples of programs CHPA thinks will solve the disposal question.

In LA County, "we came together, and made a commitment to the county that we would educate consumers in their county about proper disposal options and in LA County they felt very strongly that education needed to steer them to take back kiosks that are existing in the area," Melville said.

"So we started that project and we've been doing a lot of communication in LA County on billboards, on busses and using digital media to educate consumers."

The drug industry took a similar approach in Cook County, partnering with the sheriff's department for a program that will launch in 2017.

CHPA also educates consumers online through its "Know Your OTCs" program on preventing abuse of medication. The program's website features a section on proper disposal of OTC drugs.

The association also promotes drugstore chain Walgreens' participation in voluntary takeback efforts, as the retailer established hundreds of collection kiosks in its pharmacies around the US, Melville said.

"We are optimistic this is a more conventional, effective and cost-effective option," Melville said of its work with municipalities, adding that CHPA plans to promote this approach more aggressively in 2017.

"This issue is not going away any time soon. There are proponents from the environmental perspective who believe that any disposals in municipalities is inappropriate. We disagree. The science doesn't support that there is any impact of medicine disposal in household trash on the environment or humans," he said.

"So we will challenge those believe and assumptions and we will support alternative approaches that we believe will be embraced more fully by consumers, that are more cost effective and more convenient."

From the editors of Tan Sheet. Published online January 6, 2017

FDA's ANDA Approvals

SPONSOR	ACTIVE INGREDIENT	DOSAGE; FORMULATION	APPROVAL DATE
Sagent	Cefepime HCl	EQ 1 gm base/vial and EQ 2 gm base/vial; injectable	1/4/2017
Aurobindo	Levetiracetam sodium Cl	500 mg/100 mL (5 mg/mL), 1000 mg/100 mL (10 mg/mL) and 1500 mg/100 mL (15 mg/mL0; injectable, I.V. infusion	1/4/2017
Alkem	Finasteride	5 mg; tablet	1/5/2017
Alkem	Finasteride	1 mg; tablet	1/5/2017
Akorn	Desoximetasone	0.05%; topical cream	1/6/2017
Ajanta	Duloxetine HCl	EQ 20 mg base; EQ 30 mg base and EQ 60 mg base; delayed-release capsule	1/6/2017
Stason	Aripiprazole	2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg; tablet	1/9/2017
Invagen	Atorvastatin calcium	EQ 10 mg base, EQ 20 mg base, EQ 40 mg base and EQ 80 mg base; tablet	1/9/2017
Lupin	Desoximetasone	0.25%; topical cream	1/9/2017
Akorn	Olopatadine HCl	EQ 0.1% base; ophthalmic solution/drops	1/10/2017
County Line (Alvogen)	Acetaminophen/ butalbital; caffeine	325 mg/50 mg/40 mg; tablet	1/10/2017
Lupin	Desoximetasone	0.05%; topical cream	1/10/2017
Wash Univ School of Med	Choline C-11	4-33.1 mCi/mL; injectable, intravenous	1/10/2017
Tentative Approvals			
PharmaCare	Atazanavir	150 mg and 200 mg; tablet	1/9/2017
Anchen	Memantine HCl	7 mg, 14 mg, 21 mg and 28 mg; extended-release capsule	1/9/2017
Watson (Allergan)	Tadalafil	2.5 mg, 5 mg, 10 mg and 20 mg; tablet	1/10/2017

FDA's Rx Promo Citations Rise Slightly In 2016; Investigational Drug Promos Scrutinized

BRENDA SANDBURG brenda.sandburg@informa.com

For much of 2016, FDA seemed on pace to issue a record-low number of citations for Rx advertising, but in an end-of-year flurry, the agency issued six enforcement letters, bringing the tally to 11 – two more than the agency's Office of Prescription Drug Promotion issued in 2015. That figure was a record low, which FDA retroactively matched for 2014 when it withdrew a letter to Pacira Pharmaceuticals Inc. regarding the promotion of *Exparel* (bupivacaine liposome injectable suspension).

The agency withdrew the Pacira letter in settling a lawsuit over FDA's interpretation of Exparel labeling.

The slight uptick in 2016 follows a steady decline since the agency's 51 enforcement letters in 2010 (*see chart*). The number has fallen even more sharply since 1998, when the office issued 157 warning and untitled letters.

Asked last year about the drop in citations, FDA said that reviewing the number of compliance actions that the agency takes within a year timeframe does not take into account the work that OPDP does on other priorities to assist companies with compliance, such as policy and guidance development and core launch reviews. "OPDP uses a risk-based approach to carefully allocate its resources among these activities to have the greatest beneficial health impact," the agency said.

However, the enforcement letters issued in 2016 suggest that FDA has been looking at a broader range of issues. Four companies were cited for promoting investigational drugs and two for TV ads that communicate serious risk information while distracting visuals appear on the screen.

Nikki Reeves, a partner at King & Spalding, said FDA is taking a more measured approach to enforcement actions and is moving away from citing off-label promotions and claims in the wake of successful First Amendment challenges to such actions.

Reeves noted that FDA also seems to be focusing on promotional material where it believes there is a minimization or omission of risk information. "It will be much more difficult for a manufacturer to successfully challenge FDA enforcement action taken on the basis of minimization of risk information," she said.

'CAUTIONARY TALE' IN TV AD CITATIONS

The letters regarding direct-to-consumer TV ads, issued to Sanofi and Celgene Corp. on Dec. 12, are particularly notable. While FDA has previously criticized TV ads for obscuring risk information with audio and visual messages, these letters are unusual in focusing solely on this issue.

The Sanofi direct-to-consumer TV ad for *Toujeo* (insulin glargine) showed a man dancing to the song "Let's Groove" as he was cooking, walking his dog, mowing his lawn, and picking tomatoes with his children. And Celgene's ad for its plaque psoriasis drug *Otezla* (apremilast) showed people taking selfies at a park and dancing at a rooftop party.

These letters are "a cautionary tale for companies looking to continue doing broadcast ads," Reeves said.

FOCUS ON INVESTIGATIONAL DRUG CLAIMS

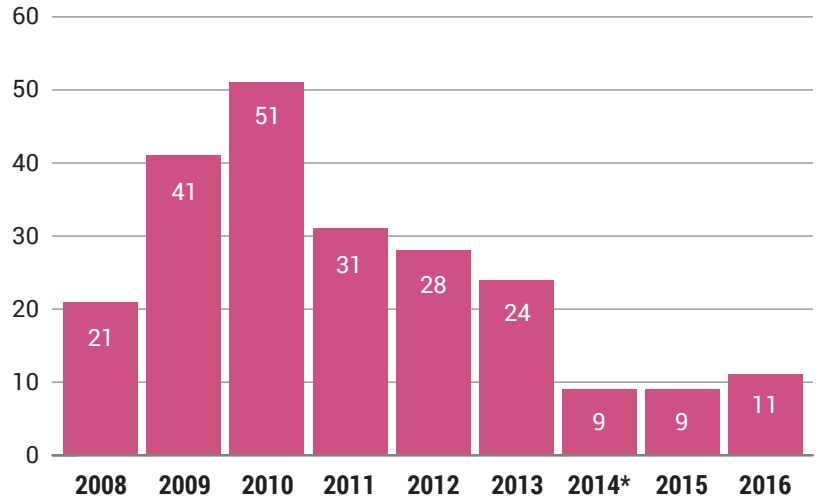
FDA objections to promotions for investigational drugs also stands out. The last letters issued for the year, dated Dec. 21, went to Chiasma Inc. and Zydus Discovery DMCC for YouTube videos posted on their websites.

In its letter to Chiasma, FDA said a video in which experts discuss new advances in acromegaly suggests that Chiasma's investigational new drug *Mycapassa* (octreotide) is safe and that its effectiveness has been proven in clinical trials.

The enforcement action comes after FDA issued a "complete response" letter for Mycapassa. In an April press release, Chiasma reported that FDA had told the company it did not believe the Mycapassa application had provided substantial evidence of efficacy to warrant approval of the drug and that Chiasma would have to conduct another clinical trial.

Mycapassa is an oral reformulation of Novartis AG's *Sandostatin*, which originally had to be injected subcutaneously three times a day. Novartis later introduced a monthly intravenous formulation

OPDP Enforcement Letters



*FDA withdrew a 2014 letter to Pacira Pharmaceuticals

The letter to Zydus cites a video about the mechanism of action of its diabetes investigational drug *Lipaglyn* (saroglitazar). FDA says the claims and presentations in the video make conclusions that the drug is "indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes mellitus," is "superior" to other molecules, and is not associated with many serious risks that are generally attributed to these other molecules with similar mechanisms of action.

FDA acknowledges that saroglitazar has been approved for use in another country – it was approved in India in 2013 – but it says the claims and presentations in the video, including the broad statements regarding the drug's approval as the "world's first," suggest that the drug is approved throughout the world, including in the United States.

FDA sent another letter citing investigational drug promotions in September to Durect Corp. and Pain Therapeutics Inc. for their *Remoxy* (oxycodone controlled-release) websites suggesting the investigational drug is safe and effective. The agency cited "considerable public health concerns" about the promotions. Pain Therapeutics subsequently reported that it had received a complete response letter from FDA requiring new studies and data to support Remoxy abuse deterrent claims.

Celator Pharmaceuticals Inc. (now Jazz Pharmaceuticals PLC) was dinged for a placard at the American Society for Clinical Oncology annual meeting describing the company's investigational high-risk acute myeloid leukemia candidate *Vyxeos* (cytarabine/daunorubicin) liposome injection. FDA said the placard and area surrounding the display did not indicate that the drug product is investigational.

In recent years, the agency has rarely issued citations for promotional pieces about investigational drugs. In 2015, OPDP sent one such letter, to a researcher at the University of California at Los Angeles' Semel Institute for Neuroscience & Human Behavior about a drug being investigated for use in brain PET scans to diagnose traumatic brain injuries, Alzheimer's disease, and other neurological conditions. And in 2013 the agency sent a letter to CBA Research Inc. objecting to a website promoting an investigational cancer drug as safe and effective.

"In recent years, FDA has rarely issued citations for promotional pieces about investigational drugs. In 2015, OPDP sent one such letter.

WEBPAGE FOR CODEINE COMBO LACKS RISK INFO

The other end-of-year letters, issued Dec. 13, were warning letters to Spriaso LLC and United-Guardian Inc.

In its letter to Spriaso, OPDP said the company's webpage for *Tuxarin ER* (codeine phosphate/chlorpheniramine maleate) extended release tablets failed to communicate any risk information about the product and included claims that suggest it is safer than its competitors. The product labeling contains a boxed warning regrading respiratory depression and death, which have occurred in children who received codeine following tonsillectomy and/or adenoidectomy.

The letter also says the webpage does not disclose that the product is not indicated for pediatric patients under 18 years of age. And FDA says the company failed to submit the webpage for agency review at the time of initial dissemination, as required. OPDP requested that the company submit a plan of action to disseminate corrective messages to the audiences that received the violative promotional pieces.

Spriaso's website now only states the ingredients in Tuxarin ER. It is the Salt Lake City, Utah-based company's sole approved product. Spriaso has two other cough products in its pipeline, one is a combination of codeine and guaifenesin and the other is a combination of hydrocodone and guaifenesin.

EMAIL LINK TO PRESCRIBING INFO INSUFFICIENT

FDA's letter to United-Guardian objected to an email for its *Renacidin* (citric acid/gluconо-delta-lactone/magnesium carbonate) irrigation solution for failing to include any risk information and making false or misleading benefit claims.

The product is indicated for dissolution of bladder calculi by local intermittent irrigation through a urethral catheter or cystostomy tube as an alternative or adjunct to surgical procedures. FDA noted that it is contraindicated in the presence of demonstrable urinary tract extravasion and that the product labeling contains warnings about fever, urinary tract infection, persistent flank pain, and sepsis, among other things.

FDA noted that the email includes a link to complete prescribing information but said this does not mitigate the omission of the risk information. OPDP also said the claims that Renacidin "simplifies long-term catheter care" and has "easy 30 mL dosing and delivery" are unsupported. It asked the company to provide a plan for disseminating corrective messages.

United-Guardian President & General Counsel Ken Globus said the email was sent to urologists once in June 2016 and that the ad included in the email also had been placed in two medical journals in April 2016, running one time in each journal. The email and ads were provided to FDA at the time they were released. Globus said the company has sent FDA a formal written response with suggestions as to how it can best address the agency's concerns and will act after receiving FDA's comments.

PATIENT CO-PAY VOUCHER AMONG 2016 CITATIONS

Of the 11 letters OPDP issued during the year, three were warning letters and eight were untitled letters. In addition to the warning letters to Spriaso and United-Guardian, FDA also sent a warning letter to Shionogi Inc. for a false and misleading

"Patient Co-Pay Assistance Voucher" for its head lice drug *Ulesfia* (benzyl alcohol) which omitted risk information.

Among the other letters of 2016, Hospira Inc., a Pfizer Inc. unit, was cited for a YouTube video about its sedative *Precedex* (dexmedetomidine hydrochloride), which OPDP said omitted risks and material facts. And Supernus Pharmaceuticals Inc. received a letter for a Spanish video for its seizure drug *Oxtellar XR* (oxcarbazepine) in which an expert suggested the drug is intended for unapproved uses. FDA said the violations were "concerning from a public health perspective" because they create a misleading impression about the drug's safety and effectiveness and suggest a use for which the labeling does not provide adequate directions for its safe and effective use.

Published online January 9, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Pediatric-focused safety reviews for various products as mandated by the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act; role of pharmacogenomics in pediatric product development	Pediatric	March 6-7
Strain selection recommendations for influenza virus vaccines for the 2017-2018 flu season	Vaccines and Related Biological Products	March 9
Premarketing and postmarketing data about the abuse of Endo's *Opana ER* (oxymorphone extended-release), and abuse of generic extended-release and immediate-release oxymorphone products	Drug Safety and Risk Management; Anesthetic and Analgesic Drug Products	March 13-14
Strategies, approaches and challenges in model-informed drug development, including use of physiologically-based pharmacokinetic modeling and simulation throughout a drug's life cycle and mechanistic model-informed safety evaluations	Pharmaceutical Science and Clinical Pharmacology	March 15

Pink Sheet

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