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FDA USER FEE BILL: House Cmte. Makes Technical Changes, Adds Pricing Resolution

SUE SUTTER sue.sutter@informa.com


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The House Energy and Commerce's mark-up of user fee legislation for the US FDA on June 7 reflects lawmakers' ongoing, laser-like focus on ensuring the key funding measure for the agency's medical product review programs does not get bogged down in controversy.

The amended version of the FDA Reauthorization Act (FDARA) that passed the full committee on a 54-0 vote looks very much like the version reported out of the Health Subcommittee in mid-May, albeit with some technical and clarifying changes on generic drugs and tropical disease treatments, and a new regulatory pathway for imaging agents.

The amended measure also reflects a sense of Congress to work to address drug pricing concerns, although an amendment aimed at allowing Americans to import cheaper drugs from other countries was voted down.

Of the 11 amendments offered by committee members, six passed on voice votes, one was rejected on voice vote, and four were withdrawn.

In the latter category was a measure targeting abuse of restricted distribution programs, as well as two Republican-sponsored amendments on off-label promotion that generated considerable opposition from Democrats. (*read more at pink.pharmamedtechbi.com*) Their removal from consideration allowed the committee to pass a "clean" bill that now heads to the House floor.

Time is of the essence in moving the measure, which reauthorizes the prescription drug, generic drug, biosimilar and medical device user fee programs that expire Oct. 1. If reauthorization legislation is not signed into law by President Trump by the end of July, FDA faces the prospect of sending lay-off notices to thousands of employees whose positions are funded through user fees.

The Senate Health, Education, Labor and Pensions (HELP) Committee marked up its version of FDARA May 11 and, like the House panel, also avoided adding controversial measures that might slow the legislative package's passage. *(Also see "Drug Importation Blocked But Not Forgotten As User Fee Bill Clears Senate Cmte" - Pink Sheet, 11 May, 2017.)*

MANAGER'S AMENDMENT

The user fee bill that came up for full committee consideration contains several mechanisms aimed at improving generic competition, including a new program modeled after FDA's breakthrough therapy

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program. The measure would allow FDA to designate a product as a "competitive generic therapy" if the agency determines there is inadequate generic competition. The designation would entitle a sponsor to increased regulatory interactions with FDA during development. *(Also see "Breakthrough-Style Program For ANDAs Added To House User Fee Bill" - Pink Sheet, 18 May, 2017.)*

A manager's amendment introduced at the markup and adopted by voice vote makes some technical change and includes clarifying language around the 180-day exclusivity award for competitive generic therapies.

The amendment also revised language related to a requirement that tropical disease new drug applications must contain results of clinical studies that are "essential" to approval and conducted by the sponsor to be eligible for a priority review voucher. The bill that passed out of the Health Subcommittee in mid-May stated that such studies must not have been relied upon by a foreign regulator for marketing approval prior to Sept. 27, 2007.

The manager's amendment clarifies the latter provision, stating that sponsors must attest that the clinical studies "were not submitted as part of an application for marketing approval or licensure by a regulatory authority in India, Brazil, Thailand or any country that is a member of the Pharmaceutical Inspection Convention or the Pharmaceutical Inspection Cooperation Scheme prior to Sept. 27, 2007."

The amendment also added manufacturers to a provision that increases penalties for sale and distribution of counterfeit drugs.

IMAGING DRUG PATHWAY

The committee adopted an amendment aimed streamlining the approval of existing contrast imaging agents for new uses if those uses are described in the labeling of an applicable medical imaging device.

"Innovations in medical technology have led to new uses for many previously approved contrast agents," said Rep. Scott Peters, D-Calif., who sponsored the amendment, adding that the measure "creates a clear, predictable FDA regulatory pathway" for expanded use of such products.

'SENSE OF CONGRESS' ON DRUG PRICING

Drug pricing concerns were brought to the forefront by several amendments, including one from Rep. Janice Schakowsky, D-Ill., expressing the "sense of Congress on lowering the cost of prescription drugs."

> An approved amendment revises language related to a requirement that tropical disease NDAs must contain results of clinical studies that are "essential" to approval and conducted by the sponsor to be eligible for a priority review voucher.

The amendment states that the Health and Human Services (HHS) secretary should commit to engaging with Congress to take administrative actions and enact legislative changes that "will lower the cost of prescription drugs for consumers and reduce the burden of such cost on taxpayers." Such actions should balance the needs to encourage innovation and improve affordability, and should "strive to increase competition in the pharmaceutical market, prevent anticompetitive behavior and promote the timely availability of affordable, high quality generic drugs and biosimilars."

"Despite repeated calls for action from the American people, we have not been able to have a real conversation about how to solve this crisis," Schakowsky said. "It is time for this committee to do what the American people are asking for us to do and work together to find solutions to lower the price of prescription drugs."

"This crisis cannot be solved by simply bringing more generics to market," Schakowsky continued. "We need a comprehensive solution that increases transparency, lowers prices for patients and the public insurance programs, and ensures that every American can get access to the drugs that they need."

Committee Chairman Greg Walden, R-Ore., who heard repeated calls from Democrats to hold a hearing dedicated to drug pricing, said he was willing to accept the amendment. However, he and other Republicans repeatedly pointed to provisions in the user fee bill aimed at bring down drug prices, including measures to increase generic drug competition and improve the predictability and timeliness of drug reviews.

"Indeed, today we have an opportunity to move legislation forward that deals with drug prices," Walden said.

IMPORTATION AMENDMENT FAILS

An amendment offered by Rep. Peter Welch, D-Vt., to allow drug importation also spurred an extensive discussion about US drug pricing before falling to defeat in a voice vote.

Rep. Buddy Carter, R-Ga., a pharmacist, said issues around drug pricing need to be dealt with internally in the US, not by looking abroad for cheaper drugs. Carter said he had a commitment from Walden and Rep. Michael Burgess, R-Tx., who chairs the Health Subcommittee, to tackle drug pricing issues further.

Carter also took aim at the pharmaceutical industry's preferred target for complaints about high drugs costs – pharmacy benefit managers (PBMs). Drug manufacturers have increasingly sought to cast insurers and PBMs as villains in the drug pricing debate, citing research that more than one-third of the list price for branded drugs is rebated back to payers and the supply chain. *(Also see "Best Defense Is Good Offense: PhRMA Wants PBMs To 'Share The Savings'" - Pink Sheet, 6 Apr, 2017.)*

The most effective and quickest way to address prescription drug prices is through scrutiny of PBMs, which "bring no value to the system," Carter said.

Walden suggested the Energy and Com-

merce Committee will look at drug pricing issues as part of a broader examination of costs across the healthcare system.

"It's not just drugs," Walden said. "What we have to look at is one end of the healthcare system to the other. What's driving up the costs of healthcare and where is the squeeze? Whether it's in the hospitals or the pharmacies or the doctors or the PBMs or the you name every piece of it. My commitment is we're going to look at every piece of this."

The Senate HELP Committee will hold a hearing June 13 on how the drug delivery system affects the prices patients that pay. *(Also see "The US Drug Pricing Hearing Pharma Wants" - Pink Sheet, 6 Jun, 2017.)*

REMS ABUSE AMENDMENT PULLED

The bipartisan support for the general idea of making drugs more affordable was not enough to overcome concerns about an amendment offered by Welch aimed at preventing brand companies from using Risk Evaluation and Mitigation Strategies (REMS) to block access to reference drug samples for generic drug bioequivalence testing.

In introducing the amendment, which is based on the FAST Generics Act and has bipartisan support, Welch said he planned to withdraw it before a vote but hoped the committee would pass it in the future.

Walden said there were some issues with the amendment that "we felt needed some additional work." However, the chairman expressed interest in working with Welch on trying to reach common ground.

Despite expectations that legislation aimed at incentivizing new antibiotics and requiring pediatric studies of cancer drugs based upon molecular target might be attached to the user fee bill, no amendments on these issues were offered at the markup. *(Also see "Off-Label Discussion, But No Additions, For House User Fee Bill" - Pink Sheet, 18 May, 2017.)* Nevertheless, several committee members spoke in favor of the pediatric cancer measure, known as the RACE for Children Act.

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Can US FDA Save Pharma From Price Controls?

MICHAEL MCCAUGHAN pinkeditor@informa.com

When people talk about administrative action to control drug pricing, they don't usually think of FDA, the agency that always says cost is not part of its mission.

That is changing fast.

FDA Commissioner Scott Gottlieb has made addressing concerns about high prices an important and somewhat surprising theme of his first weeks on the job at FDA. During the confirmation process, he noted the important role that FDA plays in ensuring competition – especially in the generic drug space – but also declined to discuss his past positions on drug pricing more generally. He said he would decline to discuss topics outside of "FDA's purview." *(Also see "Drug Pricing Pundit Gottlieb Likely To Stay In His Lane At FDA" - Pink Sheet, 14 Apr, 2017.)*

But, starting with his first address to FDA staff, Gottlieb has embraced the aspects of drug pricing that do fit in FDA's mission with gusto – building on a theme articulated by his predecessor Robert Califf. "I know FDA doesn't play a direct role in drug pricing. But we still need to be taking meaningful steps to get more low cost alternatives to the market to increase competition and to give consumers more options," he said. *(Also see "Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff" - Pink Sheet, 16 May, 2017.)*

Gottlieb followed up by promising a drug pricing "action plan" during his first Congressional appropriations hearing May 27. The focus remains squarely on encouraging generic competition, but will include steps to look at "gaming" of the system by brand name companies.

Gottlieb followed up with an interview with Bloomberg news expanding on ideas to enhance generic drug competition, including

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> At a minimum, FDA's actions are sure to be a part of the proposals that emerge from HHS Secretary Tom Price's "listening sessions" on drug costs.

prioritizing second- and third-generics, not just first-generics.

At the same time, FDA is preparing for some landmark approvals in the biosimilar space, with proposed versions of **Genentech Inc.**'s *Avastin* (from **Amgen Inc.**) and *Herceptin* (from **Mylan NV**) heading to advisory committee on July 13. That should bring renewed attention to the potential for biosimilar competition to start to impact specialty drug spending trends.

For the biopharma industry, the only question is whether Gottlieb's embrace of drug pricing will be enough to defuse calls for more direct action to bring down prices – like the perennial calls for Medicare "negotiation," embraced by President Donald Trump.

One quick gauge of the political appetite for a pricing fight will be the Senate HELP Committee's hearing on pricing scheduled for June 13. That hearing seems as though it will be structured in the best possible way for pharma manufacturers, but any high-profile event about pricing carries inherent risks for industry.

At a minimum, FDA's actions are sure to be a part of the proposals that emerge from HHS Secretary Tom Price's "listening sessions" on drug costs. Beyond the generic/biosimilar competition pieces, there could also be more streamlining on the new drug review side in the name of cost control, as well as some additional steps to open up the rules for communication with payors and medical professionals about off-label uses of medicines. *(Also see "HHS Action On Drug Pricing: Here's Who Secretary Price Is Listening To" - Pink Sheet, 25 May, 2017.)*

But would a package of FDA-focused actions really be enough for President Trump to declare victory on drug pricing? That may be too much to hope for. For one thing, while Gottlieb's plan has drawn plenty of attention in the political and investor press, Fox News has said nothing so far about FDA taking care of the pricing problem.

From the editors of the RPM Report. Published online June 6, 2017

FDA's NDA And BLA Approvals: Gleolan, Norvir Powder, Fibryna

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				
NX Development	*Gleolan* (aminolevulinic acid HCl)	1,500 mg lyophilized powder of the fluorescing agent for oral solution, for use as an optical imaging agent in patients with glioma (suspected World Health Organization Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery.	P, 3	6/6/2017
Abbvie	*Norvir* (ritonavir)	Oral powder of the protease inhibitor which can be mixed into soft foods or liquids, and used in combination with other antiretroviral agents for the treatment of pediatric patients with HIV-1 infection.	S, 3	6/7/2017
New Biologics				
Octapharma	*Fibryna* (fibrinogen (human))	Treatment of acute bleeding episodes in adults and adolescents ≥ 12 years of age with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.		6/7/2017

KEY TO ABBREVIATIONS

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

INTERVIEW: Clinuvel, A Company That Does The Unusual

MAUREEN KENNY maureen.kenny@informa.com

Clinuvel Pharmaceuticals Ltd. is a company that does the unusual.

Its novel systemic photoprotective product, *Scenesse* (afamelanotide), obtained EU approval at the end of 2014 under exceptional circumstances. There are no scientific instruments to quantify and measure the impact of the disease Scenesse treats – the rare genetic skin disorder erythropoietic protoporphyria (EPP) – or indeed the impact of the therapy itself. Scenesse was the first product where patients' views and experiences were formally integrated into the European Medicines Agency's decision-making process. Also unusually, Clinuvel has adopted a uniform global pricing policy for the product.

Last but not least, Clinuvel is a company that speaks its mind, most recently in regard to an important recent development that means Scenesse should be reimbursed across Germany, the largest European market for the product.

Clinuvel Chief Executive/Managing Director Philippe Wolgen has accused the German National Association of Statutory Health Insurance Funds (GKV-SV) of leaving "no stone unturned in its attempt to end the existence of Clinuvel." In the Australian company's May newsletter, Wolgen says insurers are "coordinating efforts internationally to cull health care costs, and will come up with any conceivable argument to lower prices of pharmaceuticals." The GKV-SV, he says, is "leading European insurers in curtailing the position of pharmaceutical companies."

The *Pink Sheet* interviewed Lachlan Hay, Clinuvel UK's general manager and, like his boss, a straight talker. Among the topics covered were the company's pricing strategy, the broader importance of getting an agreement on coverage in Germany, its ongoing frustration with UK health technology assessment body NICE, the status of the product in the US, and the need for regulators, health technology assessors and payers to listen more to patients and physicians.

Shortly after our interview, at the company's UK offices in Leatherhead, just south of London, there was another positive development for Clinuvel. To determine whether the product should be made available under the National Health Service in England, NICE will assess Scenesse as a highly specialized technology. Clinuvel had been arguing for this approach for a long time, disagreeing with the NICE view that the product was eligible for review only under the mainstream single technology appraisal pathway.

Scenesse is available in Germany, Austria, the Netherlands, Italy and Switzerland. It will be some time before a NICE decision is made regarding England. In the meantime, Clinuvel is in market access talks with "a small number of Scandinavian countries", where, says Hay, "there is certainly demand for the product".

The following Q & A is an abridged and edited version of the interview.

PRICING

Clinuvel has said the annual cost of therapy with Scenesse ranges from €56,404 ($63,546) to €84,606 ($95,355) per EPP patient per annum.

PINK SHEET: You've got a single, uniform European price and you won't budge on that. Is that correct?

Lachlan Hay: It's not so much that we won't budge on price, we've set a very transparent price for all countries, treating all expert centres equitably. All of these [health technology assessment/pricing/reimbursement] agencies say to me, I want transparency, I want to know what everyone else is paying, and I said, OK that's the price and we can structure that way. We've said from day one… that there will be no arbitrage across countries.

It's bizarre to them. They've not seen this before. I think there's a certain element of disbelief. [They think:] "Okay, what you're saying publicly is this but really we think you're doing this."

There's an expectation that something is happening behind closed doors, confidentially between company and payer. We've said from the get go, there will be one price and no discounts, no backroom deals, no incentives off the record, it needs to be fair access and transparent and that's what we're living up to.

We didn't take the decision lightly but I think our genuine execution and straightness reflects how we've done things over an extended period of time.

GERMANY

Clinuvel announced in April that it had reached an agreement with the GKV-SV that should result in all state insurers (Krankenkassen) covering Scenesse.

Germany will be your biggest market. This must be a major development for Clinuvel. Is that correct?

Hay: Absolutely. But also, Germany is a reference country [and] the GKV process is held up as being one of the higher-end processes. A lot of people will look to that and say, this is a point

> "It's bizarre to them. They've not seen this before. I think there's a certain element of disbelief." – Lachlan Hay, Clinuvel UK

of reference for us and if they've gone through that process and arrived at an agreement with GKV then I think that we can make that [work for us].

It's a twelve-month process basically. We went through the process [required under AMNOG, the German Pharmaceuticals Market Reorganisation Act]. There was a series of discussions, then that process went to arbitration and now we have the outcome.

It was a very transparent, structured process that they'd put in place. They said to us, this process will happen and this process will happen and this process will happen. It's very much stepped out, that doesn't exist here [in the UK].

SCENESSE AND EPP

Patients with erythropoietic protoporphyria, a rare genetic skin disorder, risk second-degree burns, swelling and burning if they are exposed to daylight. Clinuvel's Scenesse (afamelanotide) works by increasing the melanin content of the skin without having to expose it to the damaging effects of ultraviolet radiation. The benefits of treatment are a reduction in light sensitivity and a consequent – but limited, according to the European Medicines Agency – increase in the time patients can spend in daylight or sunlight. No other treatments are available for the condition. The product was approved in the EU under exceptional circumstances at the end of 2014.

Partly because of the difficulty of conducting clinical studies in patients who can see the results, ie pigmentation changes, and also because patients are understandably unwilling to expose themselves to sunlight-associated pain as part of a clinical trial, Scenesse required a shift in how regulators reviewed the product, including greater consideration of patient testimony during the approval process.

The company hopes to market the product in the US but has yet to file for approval there.

Why do you think that is?

Hay: To be fair, to have a very structured system like that and [put] really structured timelines in place is difficult. I mean these guys look at what, 50 or 60 drugs a year perhaps? New products. As part of that, they need to be able to plan their work but at the same time, national horizon scanning and these sorts of processes should be able to cut it down.

CALCULATING THE NUMBERS AFFECTED

Payers like certainty. In Germany, your largest market, you say between 500 and 1,090 adults could benefit from treatment with Scenesse. That's quite a wide range, isn't it?

Hay: There is always uncertainty when you're dealing with orphan indications and EPP is poorly understood still, even having worked with it for a decade. What we try and do is give the absolute worst-case scenario.

When we started out working with orphan products, the payers weren't really sure what to do either. I think perhaps on several occasions they've been burnt by an orphan drug company, where [they were given an estimated number of patients] and then what they ended up paying for was triple [that].

When you are talking about medicines that have a high cost … you try to provide them with a realistic range. How do I come to a number of between 500 and 1,900 for Germany? I try and be as precise as I can. We give very clear estimates, so here in the UK we think there are 513 EPP patients who would be eligible for treatment.

What you try and do is take your known patient numbers, you take estimates from your treatment centers, you take estimates from your patient association, you take prevalence data and throughout all of that you come to a number and it's only fair to provide a range. Now the narrower the range, the better it is. For EPP this is an ultra-orphan disease, so we're not even talking tens of thousands of patients in most instances, we're only talking hundreds or thousands.

We speak to the physicians, the treating physicians and the academic physicians and say to them, what do you think of this number? What do you make of these prevalence numbers? Is the prevalence number for country x applicable to your country?

Again, that's something that you then have to convey back to authorities and sometimes they get it right and sometimes they get it wrong. Here in the UK, for example, I would argue that they got it wrong and we've had a bit of a back and forth with them on that but costing us and the patients 16 months of delay.

ASYMMETRY

What's the basic problem regarding getting orphan drugs on to the market in Europe?

Hay: The mandate existing in Europe as a concept for approval of [orphan] products doesn't filter down… to a national

level in terms of pricing.

At a national level… all of a sudden, from a pricing perspective, you go through another review, a completely new review of your dossier despite the European [Medicines] Agency saying, well we see that there are no tools available, we accept that, we've spoken to patients. To have to go through this again, it's a frustration to put it mildly.

[I think the EMA is] trying to improve the tools that exist for the review of orphan products. Our case is certainly a good one from that regard … it took them long enough, but for the first time they started talking to patients directly as part of the process. We said to the EMA for nine years, you need to speak to patients. We said it back in 2005 when we were building the program. It [only happened] in 2014 but we got there. *(Also see " INTERVIEW: Clinuvel's Philippe Wolgen on Scenesse and the patient factor " - Scrip, 17 Feb, 2015.)*

There's an asymmetry between a company and a regulatory authority in that we've done this for 12 years, we know our drug, we know our disease indication, we know the experts who will handle it and by and large, our scientific folks have become experts, respected experts, in this disease over one or two decades.

Now I walk into EMA and they're generalists. It may be that they've got a dermatologist or a gastroenterologist who sits on the board that's reviewing but the reality is they've never seen one of these patients before. Perhaps it's unfair to expect them to have that same level of knowledge but there needs to be an acknowledgement of that asymmetry of information. *(Also see "Diligence And Janitors Needed To Keep Europe Innovating, Says Orphan Approval Pioneer" - Scrip, 22 Oct, 2015.)*

There is a need to get [regulators more] invested in this. We have a clear responsibility and a clear drive to make this product – or whatever product it happens to be – available to a patient. I don't think there's the same level of drive from a regulatory perspective.

THE UK AND NICE

What is the situation in the UK with regard to reimbursement and availability?

Hay: We are dealing with NICE at the moment. I find it very frustrating because [there is a gap between] what NICE say publicly and what happens privately. It hasn't been a transparent process. Mistakes have been made and apologies haven't been given.

At the moment, I don't have a clear end date for a decision in England and that frustrates me but it frustrates patients even more.

We started speaking with NICE around the time the product was approved. We are still in that process so again, there's this delay. You have a product which is approved in 2014, you and I are having a conversation in the middle of 2017, the timeline

> "It hasn't been a transparent process. Mistakes have been made and apologies haven't been given."

that we received from NICE is that the product might not be available until 2019. All of a sudden, the social mandate that I get from the EMA for a 10-year exclusivity is cut down to five years. How am I supposed to react to that?

Again, it comes back to that level of expertise. I'm not saying that a pharmaceutical company should have carte blanche to do what it pleases. There needs to be a system that exists and is responsible and is transparent but I don't think we have that at the moment.

You can't expect them to be perfect but … if you say something publicly, you have to do it, that's my genuine view, and if that's not happening within any organization then there needs to be change.

Are you confident you'll get Scenesse on to the market in the UK?

Hay: I am confident that the patients want it. I am fairly confident that if a regulatory authority or a payer takes on the same approach and tries to understand the disorder – and that's what we've seen [happening] over time – the product will be made available.

What advice can you give to other companies with ultra-orphan products?

Hay: Dealing with an unknown disease [is difficult]. Even if you are sitting across the table from a physician at a reimbursement authority, they have never seen a case of this before. You need to be very clear in terms of what your disease is and what your impact is but more to the point, I think you need to be very adamant, particularly in our case, about involving the patients as part of the discussion.

I can tell you about EPP, but why not speak to a doctor who has spent twenty or thirty years trying to manage this disorder [to find out] why it is that that particular physician wants a treatment, demands a treatment?

You need to bridge that asymmetry of knowledge somehow. [That may not be possible] in the space of two or three months ... but [you have to see whether you can] at least get them to see what you've seen over a decade and try and integrate that into part of the discussion. I still don't think NICE, for example, is capable of doing that.

PATIENT REGISTERS

Clinuvel monitors the ongoing use of Scenesse in EPP patients under an indefinite post-marketing authorization program. This includes post-authorization safety study (PASS) protocols and a European EPP Disease Registry.

How is the data collection progressing under the registry? What is your interaction with the EMA, two years after approval?

Hay: There's an ongoing dialogue with the EMA at appropriate points in time. The adherence to the post-authorization program from a patient and physician perspective has been good. I think that reflects the desire of the physicians and the patients to continue with the treatment when they understand that the ongoing collection of data is to ensure the ongoing monitoring of the product and thus its maintenance on the market. There's greater compliance but there is a frustration expressed from time to time about the burden that's placed on physicians to try and capture data and the time they need to spend [during] each visit to do so while prescribing the drug under usual clinical conditions. This frustration and burden extends to the patient body at times too.

From your point of view, is that a good price to pay for getting the product on the market?

Hay: When you do have an orphan product and you are going with a program which is restricted and perhaps, as in our instance, [there is] a complete lack of tools to measure the disease or a treatment for the disease, I think monitoring ongoing safety is a great value to everybody. From a commercial perspective, perhaps it's a barrier to entry for competition but more importantly, at this point in time, it's ensuring that our product is being used in the way that we want it to be used.

THE US

Scenesse has orphan and fast-track status for the EPP indication in the US, where in July last year the Food and Drug Administration said it would allow Clinuvel to file a rolling New Drug Application for the product. *(Also see "PIPELINE WATCH: 13 Approvals, Two Filings And Two Launches" - Scrip, 10 Jul, 2016.)*

With regard to the rolling dossier, you've said in the past that you hoped to submit the first part in the first half of 2017.

Hay: That's perhaps optimistic but … we like to be aggressive in our targets. Certainly by the end of this year.

Correspondence with the FDA has been frequent during preparation of the rolling NDA filing. Again, it's a similar process. It took us 10 years to get the FDA to speak to patients. There's a learning experience that is happening on behalf of the authorities in the US and you can argue about whether it's happening fast enough but the same engagement by the regulator, a process that we went through in Europe, will have to happen in the States.

What is it that the FDA wants that the EMA didn't?

Hay: At the moment, the dossiers are different in terms of format, in terms of what they're looking for, the way that it's presented. You are dealing with different legislation but the pivotal trials that we're using are the same.

> "Let's be honest, the FDA wants to ensure that the FDA reviews drugs for Americans."

What's the key difference then?

Hay: Let's be honest, the FDA wants to ensure that the FDA reviews drugs for Americans. So that's the process that they're going to go through and you have to adhere to that.

Are you doing any additional trials in the States?

Hay: In Europe, the product is under a risk management plan and part of that is to collect ongoing safety and effectiveness data. The FDA has indicated an interest in that and would want to see some of that data. So, here in Europe we provided EMA with data from the Italian and Swiss programs that we had, so these were expanded access programs over extended periods of time and that certainly adds to the safety story and can add to the effectiveness story, depending on what's available. But I think the FDA would want to see data from the program here in Europe and in all likelihood, they'll want to replicate this work.

WORTH IT?

Has there been any point where you've thought it's not worth it?

Hay: Quite often when I speak to patients - and I do speak to a number of them - I will ask them, "Is this worth doing?" I challenge them, and it's unkind but you say to them, "Should I be treating you?" I haven't had any of them say "no" yet. So, for me, that's a real validation of the worthwhileness of this program but one of the responses that I sometimes get back is, yes, it's absolutely worthwhile for us but even more so for the kids. We've been working on a pediatric formulation and we have a Pediatric Investigation Plan in place and we're following this to arrive at a pediatric dose.

I don't, by any stretch, denigrate what's been achieved thus far, I think it's phenomenal, the folks who have worked to get this approved, but I'd like to think that we can treat children. I would like to think that we've got our first pediatric trials in two to three years.

I think once you are able to treat all of those patients that you think you can help clinically, that's success.

From the editors of Scrip Regulatory Affairs. Published online June 6, 2017

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PIPELINE WATCH: 13 Approvals, Two Filings And Two Launches
http://bit.ly/2rFAogV

Pharmacoeconomic Communications To Payers Getting Multiple Pilots By Genentech

CATHY KELLY catherine.kelly@informa.com

Genentech Inc. is pilot testing approaches to communicating pharmacoeconomic information to payers on prescription drug benefits that are "related to" an approved indication, US Medical Affairs VP Evidence for Access medical Unit Jan Hansen said.

The initiative was prompted by FDA's signal in a recent draft guidance that it will allow some variation from the approved indication in the economic information that could be provided to payers, Hansen told the International Society for Pharmacoeconomics and Outcomes Research annual meeting in Boston May 23.

The FDA draft guidance, released Jan. 18, implements a provision of the 21st Century Cures Act that relaxed the requirement that pharmacoeconomic information must "directly relate" to a drug's approved indication by saying that it must only "relate" to the indication. *(Also see "Payer Communications Safe Harbor Should Extend To Off-Label Uses – Industry" - Pink Sheet, 18 May, 2017.)*

FDA also proposes that manufacturers disclose any "material differences" with approved labeling in its communications with payers.

"I think we will be stewards of good science and disclose what we think is important for payers and the agency and others to know," Hansen commented. To help establish internal procedures for implementing the requirement, "we have pilots in our company underway that will go through rigorous pressure tests to see how we do with this. We've got about five different pilots testing new approaches we've developed based on the draft guidance and the 21st Century Cures legislation."

The goal of the pilots is to "test our own internal guidance and processes for how we develop and approve promotional health care economic materials based on our interpretation of the 21st Century Cures Act," Hansen added in an email. "We hope these pilots will help us leverage [healthcare economic information] in new ways as we continue to engage in important discussions with all stakeholders in the healthcare community."

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> "The hope is that the commentary and input [FDA has] gotten will further refine their thinking and we won't have to wait another 20 years to get another set of refinements to this guidance. But the reality is, we might."

Communications using variations on approved labeling might include an economic analysis addressing a subgroup of the population studied in clinical trials on a drug, Hansen noted at the meeting. Similarly, a published study could be incorporated into an economic model that includes a patient population that differs from that in the pivotal trial but would be focused on the same indication, she added.

Bristol-Myers Squibb Co. VP and Head of Strategic Care Marketing Laurent Carter suggested another way of implementing the "related to" provision. An oncology drug approved for eight cycles of therapy could be evaluated in varying numbers of cycles in a study on cost effectiveness because there is variation in the real world, he pointed out.

"This new guidance gives us far more latitude to be able to very clearly incorporate that kind of information in the study and the communications that we're making. But it also asks us to be very explicit in terms of carrying out what those variations are."

Carter pointed out, however, that FDA's requirements on what constitutes a "fair and balanced" presentation of data may go too far. In addition to requiring information on "material differences" from approved labeling, the agency proposes that manufacturers disclose any "relevant" information or study that was considered but not disclosed in the analysis.

"If you look at that laundry list of things they are asking us to include, it's the classic FDA definition of 'fair and balanced,' which means 15 pages of qualifying information for two pages of content. I think that is the issue most organizations will wrestle with in terms of what is fair and balanced and what is appropriate disclosure." Carter predicted solutions will "vary from organization to organization" depending on "the perception of risk and the amount of risk they are willing to take."

Bristol-Myers is generating a "template" approach to all the disclosure parameters "to make sure we are addressing them, if they are applicable, to our materials going forward."

The requirement that companies disclose all relevant studies considered but not included "has probably created the most debate among our legal, regula-

tory, commercial and [health economic and outcomes research] HEOR colleagues," Genentech's Hansen pointed out. "What is the right balance? Because they want everything, every study you omitted. Come on, really?"

Instead, she suggests, "we should have summary disclosure statements, the templated approach. And if you really need the information, request it from us, like data on file." There are "ways that we can be creative with the agency, even informing them of the extent to which it is difficult to complete HEOR studies. Once they understand that, they may understand it's not so easy for us to just provide all this information."

ECONOMIC INFORMATION PRIOR TO APPROVAL

Industry is also pushing the agency to explicitly allow manufacturers to provide payers with pharmacoeconomic information on a drug prior to approval, Hansen said. "I'm very passionate about this," she pointed out. The draft guidance allows for pre-approval discussions but does not explicitly say that pharmacoeconomic data is among the types of information that can be addressed.

The Academy of Managed Care Pharmacy has also been a leading advocate for allowing pharmacoeconomic information exchange prior to approval. The FDA user fee authorization bill is considered a potential legislative vehicle. *(Also see "'Safe Harbor' For Preapproval Information Exchange To Get Legislative Push" - Pink Sheet, 18 Jan, 2017.)* But the tight renewal deadline and congressional leadership concerns about opening up the bill to potentially divisive amendments in the charged political atmosphere over healthcare mean that free speech issues may be left out of the bill.

Hansen notes that although the section in the draft guidance on health care economic information is separate from the section on pre-approval exchange, "we've had some insight from discussions we've had that led us to believe that the health care economic information section applies to the unapproved or investigational product section."

"The Academy of Managed Care Pharmacy is a leading advocate for allowing pharmacoeconomic information exchange prior to approval. The FDA user fee bill may be a potential legislative vehicle.

She pointed out "if you're producing or presenting clinical information, presentation of what you know at the time of health care economic information, extrapolation of budget impact models or other data seems fairly low risk to add if you're already going to be talking about pricing and the clinical data that you know. That's what we recommended or suggested that we'd like from the agency and we'll see where it goes."

Most manufacturers are unlikely to recall materials produced before the draft guidance came out in January, according to the two executives.

"I don't believe most organizations will withdraw everything that has been out there previously because the fundamental interpretation of what's been passed is a broadening of what can be used as opposed to restrictions," Carter pointed out. In addition, "because of the lack of clarity previously, companies for the most party were extremely restrictive in terms of the volume and nature of" communications they released.

Hansen seconded the notion that companies have been very conservative in developing materials due to uncertainty over what FDA would allow. "In our company, one promotional piece, because of the ambiguity and some of the questions we had collectively, between commercial, regulatory, legal and the HEOR team, went through over 50 drafts before finally receiving approval," she said.

TIME TO ACT, EXECS ADVISE

Although uncertainty on a number of issues remains, the two executives maintained companies should not wait for a final FDA guidance to revise their processes for developing and disseminating pharmacoeconomic information to payers to reflect the added flexibility provided in the draft guidance and Cures Act.

"Do not wait. It's time for this information to be leveraged," Hansen advised.

"We've already waited 20 years for any commentary at all" from the agency on communicating with payers, Carter said. "The hope is that the commentary and input [FDA has] gotten will further refine their thinking and we won't have to wait another 20 years to get another set of refinements to this guidance. But the reality is, we might."

"We've now gotten a beacon to help us at least see down the path," Carter observed. "Now we can build the systems and educate" internal experts. Education is an important challenge, he emphasized. "I can't tell you how many conversations I've had with legal folks, regulatory folks and HEOR folks who never read" the law on pharmacoeconomic communications with payers. "And they were making decisions on what we can and cannot do with promotions."

"The audience is craving this information so you've got this nexus of a desire in the…payer and provider marketplace as well as legislation and regulation to open the door. So it's incumbent on us to step through."

Carter also suggested "with this new guidance, there will be a proliferation of materials that go out to the marketplace. I think it will be a competitive differentiation for certain organizations that do this right and put quality information out in the marketplace because the customers will see you differently."

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Vertex Strikes Novel Reimbursement Deal For Cystic Fibrosis Drugs in Ireland

IAN SCHOFIELD ian.schofield@informa.com

Vertex Pharmaceuticals and the Irish Health Service Executive have struck what the company describes as an "innovative" agreement that provides long-term reimbursement of Vertex Pharmaceuticals' cystic fibrosis treatment, *Orkambi* (lumacaftor/ivacaftor) and expands access to the company's other CF drug, *Kalydeco* (ivacaftor).

The "portfolio" approach could be a model for access negotiations in other countries – Megan Goulart, Vertex

The deal will also cover any future patient populations for which the drugs are approved, as well as any new Vertex products approved for these patients. There are "no other kinds of agreement like this in any other disease areas or any other countries," said company spokesperson Megan Goulart.

Under the agreement, which is effective immediately, Orkambi will be funded for all of the approximately 500 people in Ireland who are aged 12 or older and have two copies of the F508del gene mutation inherited from each parent.

In March this year, Vertex submitted an application to the European Medicines Agency for Orkambi's use in 6-11-year-olds with the same mutation, and the new agreement would cover that use too, Goulart told the *Pink Sheet*. The company is also conducting a Phase III study of Orkambi in 2-5-year-olds, with enrolment expected to be completed in mid-2017.

In the case of *Kalydeco*, funding will be extended to children aged two to five with any approved gating mutation and to patients aged 18 or older who have an R117H mutation.

The company is also studying *Kalydeco* in even younger patients (under two years of age) with the same mutations, Goulart said. "In future when it gets approved for those mutations this agreement would also automatically include those mutations."

FUTURE DRUGS COVERED

Future CF drugs from Vertex will also be covered by the deal once they are authorized for marketing. These include the new combination of ivacaftor and tezacaftor, for which Vertex announced positive top-line Phase III results in March, and which is expected to be submitted for approval in the third quarter of 2017. *(Also see "Vertex Looks To Triple Combos For CF After Doublet Success" - Scrip, 29 Mar, 2017.)*

In addition, Vertex is studying triple combinations of tezacaftor, izacaftor and a third medicine, which could be any of four "next-generation" CFTR (cystic fibrosis transmembrane conductance regulator) gene correctors that the company has in the clinic. These are VX-440, VX-152, VX-659 and VX-445. The first Phase II proof-of-concept data for these products are expected in the second half of the year, Goulart noted, adding that the Irish agreement would cover those combinations too.

MODEL FOR OTHER COUNTRIES

Goulart declined to say whether Vertex had negotiated any kind of managed entry agreement with the Irish authorities, or what the price of the products or the annual costs of treatment would be, citing confidentiality.

She did say, though, that the "portfolio" approach could be a model for access negotiations in other countries, particularly in the UK where CF prevalence rates are similar to those in Ireland. The incidence of CF in Ireland is the highest in the world, with around one in 19 people carrying a disease-causing mutation in one copy of the CFTR gene, according to Vertex.

Orkambi is currently available to all eligible patients in Austria, Denmark, France, Germany, Luxembourg and the US, while *Kalydeco* is available in 27 countries. Beyond Ireland and the UK, Vertex plans to seek reimbursement for all the major markets, although Goulart noted that the processes varied widely and so it was "really hard to predict" the outcome of discussions in each country.

Cystic fibrosis, which affects around 75,000 people in North America, Europe and Australia, is caused by a faulty gene that a child inherits from both parents. The mutation produces abnormal CFTR proteins that inhibit the flow of chloride ions and water in and out of cells, leading to the secretion of thick, sticky mucus that can cause chronic lung infections and progressive lung damage.

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Pfizer Excludes EU Biosimilar Experience From US Epoetin Application

DERRICK GINGERY derrick.gingery@informa.com

> "From our perspective we regard this particular program as an application for the US," Pfizer's Ramachandra said. "We actually did not perform a formal bridge from Europe to the US."

FDA will complete its review of **Pfizer Inc.**'s proposed epoetin biosimilar without considering nearly a decade's worth of experience with the product in Europe, even though it is available and the company acknowledged the product is heavily related to its EU-approved counterpart.

Agency reviewers do not have access to data on the European-approved version of the company's proposed biosimilar of **Amgen Inc.**'s *Epogen/Procrit* (epoetin alfa) because Pfizer's subsidiary **Hospira Inc.**, which developed the biosimilar application, did not establish the scientific link between the two products and its proposed US biosimilar, which comes from the same cell line and drug substance.

The move irked some members of the Oncologic Drugs Advisory Committee, who hoped to gain some more confidence in Hospira's epoetin by looking at EU data on immunogenicity reactions during their May 25 review of the product.

Julia Lewis, a nephrologist and professor at the Vanderbilt University School of Medicine, seemed particularly concerned about why the EU data was not being offered.

"Of course it would be wonderfully reassuring to look at all that European data and say that nobody had a hypersensitivity reaction," she said during ODAC's May 25 meeting on the epoetin biosimilar. "But there is some reason why you are not having us extrapolate to that."

Gary Gordon, **AbbVie Inc.** VP of oncology development, the committee's non-voting industry representative, also said that the questions about immunogenicity were legitimate and that it was "unfortunate there couldn't be more integration if you will or understanding of the data from Europe."

Hospira's two clinical studies also did not discover efficacy or safety issues of note, including immunogenicity. Some minor differences in clinically inactive components were noticed, but were not considered an issue. *(Also see "Hospira's Epogen Biosimilar Appears Poised For Quick Advisory Cmte. OK" - Pink Sheet, 23 May, 2017.)*

Hospira's epoetin biosimilar has a June user fee goal. It was resubmitted in December 2016 after the company received a complete response letter. *(Also see "Pending Biosimilars" - Pink Sheet, 13 Feb, 2017.)* The firm is seeking approval of its proposed epoetin biosimilar for all four US-licensed Epogen indications based on analytical characterization, non-clinical data, and safety and efficacy data in patients with chronic kidney disease.

ADVISORY COMMITTEE VOTE

Does the totality of the evidence support licensure of Epoetin Hospira as a biosimilar product to US-licensed Epogen/Procrit for the indications for which US-licensed Epogen/Procrit is currently licensed and for which the applicant is seeking licensure? **14-1 in favor**

'SAME AS THE EU RETACRIT' DRUG PRODUCT FORMULATION

Hospira has been marketing its Epogen biosimilar *Retacrit* in Europe for nearly 10 years. But when filing for US approval, it chose not to create a three-way scientific bridge showing the EU-approved product, US-approved reference product and proposed US biosimilar were similar to each other, which would have made the EU safety experience available.

Sumant Ramachandra, Pfizer Essential Health senior VP and research and development head, told the advisory committee that the product intended for US approval was based on EU-approved Retacrit, but was a distinct product.

"From our perspective we regard this particular program as a US application for the US," Ramachandra said. "We actually did not perform a formal bridge from Europe to the US."

The company said in its briefing document for the advisory committee that its proposed US Epogen biosimilar "originated from the development" of Pfizer's EU-approved Retacrit and that the drug product formulation "is the same as the EU Retacrit [drug product] formulation."

Hospira also said that the engineered Chinese hamster ovary cell line used to produce the drug substance is the same as that used to produce EU-approved Retacrit drug substance.

"The [drug substance] manufacturing process for EU Retacrit was transferred to a larger scale manufacturing facility in the US and was validated to support the Epoetin Hospira program," the company said in its briefing document. "The cell culture, harvest and purification steps used to manufacture the Epoetin Hospira [drug substance] are the same as those for EU Retacrit with minor modifications to enable production at a larger scale."

Ramachandra also told the committee that its post-marketing surveillance apparatus for immunogenicity adverse events is based on Hospira's experience in the EU, while still reminding them that the products were not related.

"Based on our extensive experience in Europe, we recognize that the rates do occur at a baseline rate, but we want to make sure it is captured if any cases do arise," he said. "We have about 363,000 patient years of experience in Europe with the EU Retacrit. I do want to point out that the EU program is considered distinct from this program, even though it is highly related. I want to be respectful to that."

One potential issue that a bridge may not have been established is a difference in manufacturing requirements separating FDA- and EU-approved Epogen biosimilars.

EU-approved Epogen was reformulated several years ago to remove a human serum albumin stabilizer to respond to concerns about transmission of variant Creutzfeldt-Jakob disease. FDA did not order the same change, creating differences between the US and EU reference products. *(Also see "Biosimilars Missing In Action: FDA, Sponsors Quiet About Pending Applications" - Pink Sheet, 27 Jul, 2015.)*

Indeed, because of the difference, a similarity comparison to create a bridge between the US- and EU-approved Epogen products may not have been possible or much more difficult.

FDA ONLY SAYS NO BRIDGE ESTABLISHED

Donald Mager, a pharmaceutical sciences professor at the University of Buffalo, acknowledged that Hospira's epoetin biosimilar for US approval was a separate product, but still asked FDA if there were any new safety signals that have emerged with Retacrit in Europe.

R. Angelo de Claro, medical officer and team leader in the FDA Office of New Drugs' Division of Hematology Products, said the agency's approach to the review was that the EU-approved biosimilar was related, but not the same as the proposed US biosimilar.

De Claro said the agency can rely on non-US comparators for its review, but "in this case, FDA does not have the complete scientific bridge in order to rely on the European data."

"The scientific bridge … would have consisted of not just analytical, but also clinical pharmacology and clinical data to establish the relationship between the European product, the proposed biosimilar and the US reference product," he said. "That was the issue that we were facing."

Lewis then asked whether the glycosylation of Hospira's EU product was different than the product submitted for US review or whether the company did not give the necessary data. De Claro responded that there was no complete scientific bridge and that the agency could not comment on proprietary information.

Ramachandra said that the cell line and

PFIZER'S REQUESTED EPOETIN INDICATIONS

- For treatment of anemia due to chronic kidney disease, including patients on dialysis and not on dialysis to decrease the need for red blood cell transfusion
- For treatment of anemia due to zidovudine administered at less than or equal to 4,200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of less than or equal to 500 mUnits/mL
- For treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
- To reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin greater than 10 to less than or equal to 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery

Source: FDA briefing documents

other Retacrit manufacturing processes were transferred for production of the US product and matched to FDA-approved Epogen.

Despite the immunogenicity questions, the advisory committee voted overwhelmingly to recommend approval of Hospira's epoetin product for all of Epogen's indications. Several also wanted FDA to ensure postmarketing surveillance. *(Also see "Biosimilar Advisory Committees Getting Smoother, Even As Worries Stay The Same" - Pink Sheet, 25 May, 2017.)*

NOT THE FIRST TO SHIRK EU DATA

While the sample size is small, FDA and its outside advisors often have been able to review EU experience when considering US approval of biosimilar products because several companies have taken biosimilars already on the market in Europe and applied for US approval once FDA opened its pathway.

Sandoz Inc. used EU experience as part of its application for FDA approval of *Zarxio* (filgrastim-sndz), a biosimilar of Amgen's *Neupogen* (filgrastim). It became FDA's first approved biosimilar. *(Also see "EU Data Helps Sandoz's U.S. Clinical Program For Filgrastim" - Pink Sheet, 12 Jan, 2015.)*

Celltrion Inc., which obtained approval of *Inflectra* (infliximab-dyyb), a biosimilar of **Johnson & Johnson**'s *Remicade* (infliximab) in 2016, also used data from a comparison to the EU-approved reference product to support its US application. *(Also see "Celltrion's Biosimilar Clinical Evidence Heavily Weighted By Ex-US Data" - Pink Sheet, 15 Feb, 2016.)*

But a number of sponsors have not had European experience to help FDA's review. Sandoz's *Erelzi* (etanercept-szzs), a biosimilar of Amgen's *Enbrel* (etanercept), was submitted while its European Medicines Agency application was under review. Celltrion also said it planned to submit applications for biosimilars of **Biogen Inc.**'s *Rituxan* (rituximab) and **Genentech Inc.**'s *Herceptin* (trastuzumab) while EMA review was ongoing. *(Also see "Celltrion's Biosimilar Strategy Includes Simultaneous EMA/FDA Reviews" - Pink Sheet, 7 Oct, 2016.)*

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French Pharma Industry Lays Out Wishlist For New Government, Proposes Five-Year Pact

IAN SCHOFIELD ian.schofield@informa.com

Philippe Lamoureux, director of France's pharmaceutical industry body Leem, says he is optimistic that the new French government will have a more positive attitude towards the industry than its predecessor – one that takes a longer-term view of the value offered by new medicines.

However, Lamoureux cautions that the healthcare sector continues to face economic and other challenges, and that the industry will need to pay "close attention" to the positions that are taken in this area by the new government once it gets down to business after the legislative elections on June 11 and 18.

Pro-business, pro-EU centrist Emmanuel Macron was elected French president on May 7. During the election campaign, he said he would support an "innovative, job-creating" pharmaceutical industry and encourage firms to conduct more manufacturing in France. He was also in favor of long-term visibility to allow companies to better plan their industrial strategies and said medicines should be paid for at a "fair price" if they were truly innovative. *(Also see "France's New President Will Support A Pharma Industry That Produces Innovation At Fair Prices" - Pink Sheet, 8 May, 2017.)*

After the election, Leem put out a statement saying that the country was facing a number of economic challenges in areas like employment, growth, competitiveness and attractiveness of the country, and that the healthcare industry represented a "sector of excellence bringing innovation and dynamism" and a "sector of the future for the national economy."

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It said that the current "unprecedented wave of therapeutic innovations" presented technological, public health, access and funding challenges, after "five years of short-term cost-containment policies" had resulted in an "economic recession for the pharmaceutical industry." The future of this "strategical industrial sector" was in the balance, it said, and expressed hope that it could establish a "sincere

and constructive" dialogue with the new government.

Since his election, Macron has appointed a new prime minister, Edouard Philippe, and a new health minister, Agnès Buzyn – a doctor who specializes in immunology and hematology and has held several posts in national scientific and research bodies.

TOO EARLY TO SAY

According to Lamoureux, it's still too early to say with any certainty what policies the new administration will follow once it is fully in place. For one thing, it is not clear what kind of parliamentary majority Macron will win when the country goes to the polls in the legislative elections later this month – although the signs are that his En Marche! party will do well, possibly gaining more than half of the 577 seats in parliament.

Lamoureux did express some optimism though: "We think the campaign declarations made by Emmanuel Macron go in the right direction. In particular, he has a very good knowledge of the economic reality of companies, and their need for long-term visibility and predictability."

However, "the economic constraints on the French social protection system remain the same," Lamoureux told the *Pink Sheet* in an interview. "there is a big deficit, and in addition the outgoing government implemented some measures that will have an impact on healthcare spending. We know already that the next PLFSS [social security financing bill] will be difficult, and we need to pay close attention to the positions taken in this area by the new government."

In the run up to the presidential elections, Leem had proposed to each of the candidates a five-year "pact" that would set out the future relations between the state and the pharmaceutical industry, Lamoureux said.

Read the full article here

These relations had deteriorated over the past five years because of the policies followed by the last government. Last year, for example, under the social security financing bill, the government said it expected to save €500m in 2017 through drug price cuts and €250m in the form of sales rebates. *(Also see "France 2017: More Price Cuts, Rebates, Generics and Biosimilars, And A New Innovation Fund" - Pink Sheet, 7 Oct, 2016.)*

"I think the state in the past few years has lost the capacity to have a vision of what it expects of our sector, and has favored short-term policies of regulation to the detriment of the industry's industrial ambitions and its ambition of innovation for patients," he declared.

But Lamoureux said Leem was "convinced" that there would now be the political will to go in a new direction, and that after "five years of policies of short-term regulation, we really hope for a change with the new administration."

Industry wanted to see "a return of the vision of what a medicines policy should look like – one that takes account of the contribution of medicines to public health, and to the modernization of the health system, and does not see medicines as simply a variable to be adjusted when balancing the social accounts," the Leem director said. "We are not just a cost but an investment. We are not only part of the problem but basically part of the solution."

> "After five years of policies of short-term regulation, we really hope for a change with the new administration"
> – Leem director Philippe Lamoureux

KEY AREAS OF CONCERN

Lamoureux outlined four areas where he would like to see progress under the new government, the first of which was access to innovation. "France has a tradition of seeking early and wide access, but this policy was weakened by the last government, and France has fallen back in this sense in the past five years. So our expectation is that France will rediscover its position as the most welcoming country in Europe for innovative medicines."

The second area was regulation, he said, noting that over the past five years, medicines, which account for around 15% of total healthcare expenditures, have provided 50% of savings in the healthcare area. "Will the next government have a more balanced policy, and will the contribution of the pharmaceutical industry be progressively reduced in line with the proportion of health expenditure it accounts for?" Lamoureux wondered.

His third area of concern is the government's industrial policy. He noted that French companies manufacture a wide range of mature medicines as well as products in niche areas like vaccines. "But in the past few years, France has found it hard to manage the production of new molecules and innovative medicines. This is a challenge of industrial attractiveness and the government needs to improve the situation."

PRICING ISSUES

Lastly he singled out what he described as a lack of efficiency at government level. There have been complaints, for example, that the French authorities are still not meeting EU deadlines on pricing and reimbursement decisions. "France traditionally has a very strong administration but nowadays it has problems in terms of efficiency – it is heavy and lacks predictability," Lamoureux declared.

In the pricing area, he said that there had been a "hardening of the dialogue on conditions of price setting by the authorities. In particular, we signed a framework pricing agreement that set out the rules of the game, but six months after the signature of this agreement, the previous government sent the president of the pricing committee (CEPS) a ministerial guidance letter that contradicted the agreement we signed. So today there is a discord between the agreement we signed and what they want the CEPS to negotiate."

The key issue here, he said, relates to the price of products with a level IV SMR (medical benefit) rating – ie, those showing what he called "incremental" innovation. "The conditions in which we ask the CEPS to open talks with companies do not match what is in the framework agreement, which has the effect of slowing down talks." This was a real challenge for the next government, Lamoureux

said. "We have asked them to bring the instructions to the CEPS in line with the agreement we have signed."

Leem will be making overtures to the new incumbents after the legislative elections. "The ministerial cabinets are not yet fully formed, but we have begun to make contact," he added.

NEW HEALTH MINISTER

It is not clear what policies will be followed by the new minister for health and solidarity, Agnès Buzyn. Until her appointment, she had been president of the French health technology assessment body HAS (Haute Autorité de Santé) since March 2016, and therefore has experience in the criteria that feed into drug pricing decisions. She has also been a member of the boards of the Biomedicine Agency, the French Blood Establishment, and the National Cancer Institute (INCa).

However, some have voiced concern that while she is familiar with areas like innovation, research and access to medicines, she has not been widely involved in politics, and has a broad portfolio that encompasses areas in which she is not so experienced, such as social solidarity and the family. The fear is that she may therefore not be able to find sufficient time to devote to the healthcare sector.

The new minister has also at times criticized the high cost of some innovative new medicines – although given the high profile of this issue, that should not come as any surprise. Macron himself has suggested that the industry should produce innovative drugs at "a fair price."

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India Facing 'Pincer-Like' Pressure On IP In Europe, Asia Trade Talks

PENELOPE MACRAE pinkeditor@informa.com

Big pharma has been up in arms for years over what it sees as India's refusal to respect intellectual property rights (IPR), and the US has long accused the country - the world's leading exporter of inexpensive generics - of being one of the worst "delinquents" in this area.

India's IPR rules are now also coming under intense scrutiny in ongoing free trade talks with the European Free Trade Association or EFTA – a bloc made up of Switzerland, Norway, Iceland and Liechtenstein – and in negotiations for a China-championed Asia pact known as the Regional Comprehensive Economic Partnership (RCEP).

"It's like a pincer attack on India. The US has been putting pressure on data exclusivity and patent linkage, Now we're seeing the same with RCEP and the Swiss in EFTA. The pharmaceutical lobbies are putting pressure through various channels," Leena Menghaney, South Asia Access Campaign head at Médecins Sans Frontières (MSF), told *Pink Sheet*.

With the US now having withdrawn from a separate planned 12-nation agreement known as the Trans-Pacific Partnership, attention is focusing on potential alternate trade agreements, specifically EFTA and RCEP, which involve India and 15 other

countries including the 10-member Association of South East Asian Nations (ASEAN).

The ASEAN nations want the RCEP negotiations to achieve "substantial" progress before year-end, as 2017 is the 50th anniversary of the bloc's founding.

Talks also resumed on May 30 in Liechtenstein between India and EFTA on a planned Trade and Economic Partnership Agreement (TEPA), against the backdrop of a document leaked by the US-based NGO Knowledge Ecology International.

The document, titled "Note by Switzerland," said India should drop its ban on patent "evergreening" and pressed India to allow data exclusivity, which would limit generic competition, according to MSF. There has so far been no comment by the Swiss government.

'BACKDOOR ROUTE' SOUGHT?

"By pushing for 'data exclusivity,' Swiss pharmaceutical corporations are trying to get a backdoor route to a monopoly - even when a drug doesn't merit a patent under India's law. This would translate into high drug prices for people across the world," Menghaney commented.

MSF takes a particular interest in ensuring access to affordable Indian generics as it uses them for its medical relief work. For example, over 97% of the antiretroviral medicines MSF buys for HIV treatment, and three-quarters of its tuberculosis medicines, are sourced from Indian generic companies.

"We hope Commerce Minister Nirmala Sitharaman will remain firm in the EFTA talks and not agree to anything beyond what's required" by the World Trade Organization's Agreement on Trade-related Aspects of Intellectual Property (TRIPS), Menghaney said.

Read the full article here

Sitharaman told India's *Financial Express* last month that there was "no basis for Western anxiety about the IPR system…Our policies are completely TRIPS-compliant."

The Swiss demands in the EFTA talks come as similar pressure has been brought to bear on India in the RCEP negotiations,

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MSF says. India is to play host to a new round of RCEP talks in July in the southern Indian city of Hyderabad.

According to a draft chapter, also leaked by Knowledge Ecology International, Japan and South Korea are pushing for "TRIPS-plus" measures that involve data exclusivity and extend patents beyond the usual 20 years.

PAST ACTION

Switzerland-based **Novartis AG** took the Indian government to court over India's 2005 Patents Act in what became a long-drawn legal battle in which the Swiss company sought patent protection for its cancer drug *Glivec* (imatinib). The fight focused on Section 3(d) of India's Patents Act which discourages the granting of patents on new forms of known medicines, effectively preventing evergreening.

Novartis lost its case when India's Supreme Court ruled in 2013 that the drug's active ingredient was already known before its development.

Among other rulings, in 2012, New Delhi also issued a compulsory license, allowing a generic company to produce a lower-cost version of **Bayer AG**'s costly liver cancer drug *Nexavar* (sorafenib). India's patent decisions have created significant friction with MNCs and have highlighted conflicts between public health and IP interests. *(Also see "India rejects Bayer Nexavar CL appeal " - Scrip, 16 Dec, 2014.)*

'RED LINES' AND IPR POLICY

However, India - which exports around $15bn worth of generic drugs globally - has said that it is clear about its "red lines" and will not go beyond what is required by TRIPS. But the US and other countries say TRIPS should be seen as a floor, not a ceiling, in IP standards and that India's patent regime has failed to keep pace with developments in areas as such as medicine and software.

The government of Prime Minister Narendra Modi last year released a national IP policy intended to speed registration of patents and generate public awareness about intellectual property. But the government stood firm against Western pressure to relax its patent laws, mindful of the fact nearly 70% of Indian healthcare expenses are paid out-of-pocket and tens of millions of Indians are pushed into poverty each year by medical expenses.

Modi, on a recent visit to Europe, has said he wants to revive negotiations on a free trade agreement with the European Union, India's largest trading partner, and is keen to boost India's exports globally. But before the talks stalled, India's IP regime had figured as a key issue, MSF noted. It urged the EU to resist pursuing "aggressive IP policies" in any new discussions.

India is among the countries most vulnerable to rising global protectionism, the IMF has warned. But even though India's economic growth depends a lot on investment and trade, New Delhi has a long reputation of playing spoiler in multilateral trade talks as it seeks to balance the competing interests of its 1.25 billion people.

RCEP WORRIES

India's many reservations about the RCEP - including worries it would lead to a flood of cheap Chinese imports - may mean New Delhi will balk at signing any deal, the China state-run *Global Times* suggested in May. The newspaper mooted the idea that Beijing might go ahead on the RCEP without India, noting that "India has unilaterally obstructed the normal process of WTO negotiations many times. In the final analysis, India is still worried about the lack of competitiveness of its local enterprises."

Meanwhile, India's free trade negotiations with EFTA and the EU have been start-stop over the last decade and they could well bog down again, observers say.

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Opana ER Should Come Off The US Market, FDA Tells Endo

SUE SUTTER sue.sutter@informa.com

The US FDA's request that **Endo Pharmaceuticals Inc.** withdraw *Opana ER* (oxymorphone extended-release) due to its intravenous abuse potential suggests the agency will take a tougher stand on currently marketed opioids under the leadership of newly installed Commissioner Scott Gottlieb.

On June 8, FDA announced it has asked Endo to pull the long-acting opioid from the market because the drug's reformulation in 2011 resulted in a shift in the preferred route of abuse from intranasal to intravenous.

The agency's conclusion that the drug's benefits no longer outweigh its risks follows a similar finding by its advisory committees three months earlier.

FDA said its action marks the first time the agency has taken steps to remove a currently marketed opioid due to the public health consequences of abuse.

While the decision to seek Opana ER's withdrawal may well have been cemented before Gottlieb took the agency's helm May 11, it nevertheless carries the new commissioner's imprimatur. The high-profile regulatory action may leave other opioid product marketers unsettled that they, too, could face the same fate, particularly given Gottlieb's vow that the agency would take a more activist role in combatting opioid abuse. *(Also see "Opioid Policy At US FDA: Gottlieb Seeks More Activist Role To Combat Abuse" - Pink Sheet, 6 Apr, 2017.)*

"We are facing an opioid epidemic – a public health crisis, and we must take all necessary steps to reduce the scope of opioid misuse and abuse," Gottlieb said in an FDA press release announcing the action. "We will continue to take regulatory steps when we see situations where an opioid product's risks outweigh its benefits,

not only for its intended patient population but also in regard to its potential for misuse and abuse."

ENDO 'EVALUATING OPTIONS'

Now that FDA has requested Endo voluntarily remove the product from the market, the ball is in the company's court.

If Endo chooses not to pull the product, FDA said it will "take steps to formally require its removal by withdrawing approval. In the interim, the FDA is making healthcare professionals and others aware of the particularly serious risk associated with the abuse of this product."

> Endo is reviewing FDA's request and "evaluating the full range of potential options as we determine the appropriate path forward."

In a statement, Endo said it is reviewing the agency's request and "evaluating the full range of potential options as we determine the appropriate path forward."

The company's statement points out that the withdrawal action is based upon safety issues resulting from misuse and abuse of the drug, not from its approved use in appropriate patients.

"Despite the FDA's request to withdraw Opana ER from the market, this request does not indicate uncertainty with the product's safety or efficacy when taken as prescribed," the company said. "Endo remains confident in the body of evidence established through clinical research demonstrating that Opana ER has a favorable risk/benefit profile when used as intended in appropriate patients."

It seems unlikely that Endo would muster a challenge to FDA's withdrawal request. The company has been de-emphasizing its branded pain portfolio in favor of other therapeutic areas, and FDA's announcement could become a commercial death knell for the product, making physicians reluctant to prescribe it and insurers reluctant to pay for it.

Fighting an FDA product withdrawal request can be a resource-intensive effort, as **Genentech Inc.** learned in its unsuccessful battle to hold onto the accelerated approval breast cancer claim for *Avastin* (bevacizumab). *(Also see "Avastin Loses Its Breast Cancer Claim; FDA's Hamburg Opts For Withdrawal Over Restrictions" - Pink Sheet, 21 Nov, 2011.)*

Such an effort also can carry significant public relations risks; in this case, Endo would be fighting to keep the troubled product on the market in the midst of an opioid-driven public health crisis.

ADCOMM FAVORED RESTRICTIONS OVER WITHDRAWAL

FDA's request for market withdrawal may have surprised some agency observers given that a majority of its advisory committee members did not recommend such a drastic step.

Following a two-day meeting in March, 18 of 27 members of the Drug Safety and Risk Management and the Anesthetic and Analgesic Drug Products advisory committees voted that the benefits of reformulated Opana ER do not outweigh its risks.

Of the 18 panelists who found an unfavorable risk/benefit profile, eight specifically called for the product's withdrawal, concluding that it offered no unique benefits compared to other long-acting opioids and that other regulatory strategies would be ineffective. The remainder suggested continued marketing was possible with revised labeling and a Risk Evaluation and Mitigation Strategy that limits prescribing by pain medicine specialists and for certain kinds of patients.

Even some of the panelists who voted that the risk/benefit profile was still favorable called for tighter restrictions on the drug's use and prescribing. *(Also see "Opana ER Looking At REMS – Or Worse – After US FDA Panel Weighs Intravenous Abuse Risk" - Pink Sheet, 14 Mar, 2017.)*

REFORMULATION BACKFIRED

The panel made its recommendations following an exhaustive review of postmarketing data that suggested the drug's reformulation has resulted in an increase in abuse by the intravenous route.

Opana ER was first approved in 2006. In December 2011, FDA approved a new formulation that incorporates a polyethylene oxide matrix intended to make tablets more difficult to crush and abuse by the intranasal or injection routes. However, the agency declined to include labeling language on abuse deterrence.

In 2012, the company began replacing distribution of original Opana ER with the new formulation. Endo petitioned FDA for a determination that the original formulation was withdrawn for safety reasons and requested the agency not allow generics that reference the original formulation. *(Also see "Endo Seeks To Block Generics Of Opana ER That Are Not Crush-Resistant" - Pink Sheet, 17 Sep, 2012.)*

In a 2013 response rejecting the petition, FDA said it found insufficient evidence to establish that the original formulation had a higher abuse potential than the new one. The agency pointed to data suggesting the new formulation it is more easily prepared for injection and said postmarketing studies suggested the "troubling possibility" that more intravenous use was occurring with the new version. FDA also rejected Endo's request for abuse-deterrent labeling.

At the advisory committee, FDA presented analyses of postmarketing epidemiological studies and other data that suggested the reformulation has caused a shift in abuse patterns from the intranasal route to intravenous administration. The panel also heard data linking Opana ER intravenous use with cases of HIV transmission and dozens of reports of thrombotic thrombocytopenic purpura. *(Also see "Opana ER: Effort To Expand US Label Might Lead To Withdrawal Due To Abuse Problems" - Pink Sheet, 9 Mar, 2017.)*

"The abuse and manipulation of reformulated Opana ER by injection has resulted in a serious disease outbreak," Center for Drug Evaluation and Research Director Janet Woodcock said in the agency's release. "When we determined that the product had dangerous unintended consequences, we made a decision to request its withdrawal from the market. This action will protect the public from further potential for misuse and abuse of this product."

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Deficient DMFs Jeopardizing Timely Approvals of ANDAs

JOANNE EGLOVITCH joanne.eglovitch@informa.com

Active pharmaceutical ingredient manufacturers should improve the quality of their Type II drug master file (DMF) submissions to speed approvals of the DMFs and the generic drug applications that reference them, an FDA official said May 24 at the Association for Accessible Medicines' Chemistry, Manufacturing and Controls Workshop in Bethesda, Md.

There is much room for improvement, according to Ramnarayan Randad, a chemist with the Office of Pharmaceutical Quality in FDA's Center for Drug Evaluation and Research: 98% of DMFs are rejected in first-cycle reviews, and multiple DMF review cycles are preventing as many as one third of abbreviated new drug applications from winning approval in their first-cycle reviews.

Randad offered tips on how to improve the caliber of submissions so that more DMFs, as well as the ANDAs they are linked to, get timely approval.

Yet a representative of the generic drug industry contends that FDA is partly to blame for this high rejection rate, saying the agency asks for information that is not relevant to the DMF and imposes impurity requirements that are above and beyond the standards set by the International Council for Harmonization and the US Pharmacopeia.

Under the Generic Drug User Fee Amendments of 2012, FDA cannot begin an ANDA review until it determines the relevant DMFs are "available for reference."

Randad said that "the good news is that 2% of the DMFs are approved in the first cycle. We have a long way to go and maybe by next year when I stand here and give a talk that number will be better." He added that "another piece of good news is that 50% of the ANDAs already have a DMF."

The "good news is that 2% of the DMFs are approved in the first cycle" and "50% of the ANDAs already have a DMF." – FDA's Randad

LONG REVIEW TIMES FOR DMFS HURTING ANDAS

FDA's analysis found that of the 521 DMFs submitted between January 2015 and June 2016, the mean response time was 161 days, or about 5.5 months, and the median response time was 133 days, or over four months. The minimum time for approving DMFs was 11 days and the longest was 667 days. This was from a recent survey of complete response first-cycle response times for Type II API DMFs.

The analysis showed that 98% of DMFs being reviewed for the first time are rejected and issued a complete response letter, and that most DMFs will receive two or three cycles of review before they can be approved.

The data further shows that the majority of DMFs, 68%, are getting a decision in 91 days or more, while a much smaller percentage are getting shorter reviews; 17% are getting decisions by 60 days or less, and 15% are getting decisions in 61 to 90 days.

The survey's finding was that reducing both the total number of review cycles and the time for response from the DMF holder is critical to increasing the chances for a first-cycle ANDA approval.

Randad said that "the first-cycle response times are currently too long to be compatible with the first-cycle ANDA approval in a 10-month or 8-month review clock."

He said that "based on our analysis, unless DMF response times are significantly reduced, it is possible that up to one-third of original ANDAs could be ineligible for a for a first-cycle approval due to an inadequate API DMF."

To shrink these timelines, he said that "both industry and FDA should strive to lower the rejection rate. As such, applicants should clearly communicate the ANDA action timeline to their DMF holder, and to make effective use of teleconferences and e-mail options for getting clarification on deficiencies so that responses are complete."

Randad also suggested that DMF holders should also avoid submitting amendments to already submitted DMFs. He said that unsolicited amendments can delay ANDA approvals.

FDA OUTLINES DEFICIENCIES

Randad discussed some of the major deficiencies behind the rejections that have impeded first-cycle approval in recently submitted DMFs. The submitted information follows the format of the Common Technical Document's Module 3 on drug substance quality.

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These are some of the problems found in Section S.2 of the CTD:

- Not reporting "hidden facilities." If the facilities need to be inspected this can take a considerable amount of time.
- Outsourcing the manufacturing process. Lack of information about the outsourced process may generate multiple deficiencies. It also raises the risk that this facility may need to be inspected, which can take a considerable amount of time.
- Having multiple vendors of intermediate materials. Reporting multiple intermediate vendors may cause deficiencies if adequate data isn't provided to show equivalent quality of material or if there are significant differences in the manufacturing processes between vendors.
- Declaring API starting materials that are unacceptable and without the necessary justification. This may result in a request to establish starting materials earlier in the manufacturing process, which Randad called a "significant amount of work." He said that "no talk at GPhA or AAM is complete without a talk on starting materials. Make judicious use of starting materials and justify them. The best pointer I can give you is use the criteria listed in ICH Q11 and do not be selective." He also referred the audience to the European Medicines Agency's "excellent" reflection paper on justifying starting materials, issued in September 2014.
- Setting high limits for impurities and intermediate specifications and having specifications that are too wide. He said that "sometimes we see the specifications that they are so wide that you can drive an 18-wheeler through them." This may result requests for spike/purge studies for impurities that are not tested in the drug substance specification.
- Not considering byproducts when discussing fate of residual intermediates. Randad said that the discussion of the fate of these materials should include data on byproducts that may form due to continued reaction downstream.
- Not addressing impurities such as regioisomers, stereoisomers, as well as longer and shorter chain analogues in starting materials. This may result in a request for that data.

These are some problems noted in Section 3 of the CTD:

- Setting limits over ICH Q3A limits for impurities without adequate justification. Randad said that safety studies for impurities above these limits will require a pharmacological/toxicological consult "which can take a significant amount of time."
- Submitting data from the comparison to the reference-listed drug using only retention times. This may result in a request for further data as high-pressure liquid chromatography is not a specific test for identification.

Problems noted in Section 4 of the CTD are the following:

- Not submitting full method validation information for USP impurities when using an in-house method.
- Submitting analytical methods that lack the needed sensitivity for their intended purpose.

The following are examples of some deficiencies in Section 7 of the CTD:

- Lack of mass balance during forced degradation studies. This raises the question of whether analytical methods are stability indicating and may result in requests to redo the study.
- Having out-of-specification results from stability studies without ascertaining the root cause.

One area of contention is that FDA reviewers have been imposing impurity thresholds that are stricter than ICH and USP impurities standards.

INDUSTRY SAYS FDA HOLDING UP REVIEWS

Yet an official representing the API industry argued that FDA shares some blame for the high DMF rejection rates.

Dan Snider, head of research and development for **Mylan Pharmaceuticals Inc.** in Morgantown, W.Va., said that the industry has some issues with how FDA is handling and reviewing DMFs. His remarks were based on a survey of AAM member companies and their experiences with FDA in submitting DMFs.

One area of contention is that FDA reviewers have been imposing impurity thresholds that are stricter than ICH and USP impurities standards.

Some examples:

- In an instance of a delay that occurred on multiple ANDAs with a third-party API supplier, OPQ requested that the DMF holder confirm that "one or more theoretical process impurities" would not be present in the final product. OPQ required the DMF holder to obtain and synthesize each theoretical impurity, then develop assay methodology capable of quantitating them at very low levels. He said that this "time-consuming" process delayed approval of multiple ANDAs by four to six months.
- Another case involved FDA reviewers asking for genotoxic impurity limits above and beyond those levels specified in ICH M7 for genotoxic APIs used in cancer drugs. Snider said that "this raises the question of why there is not alignment with ICH guidances. And why have the ICH guidance and the USP become thought of as minimum standards?"
- In another case, a generic launch was delayed because the DMF review branch continued to send out DMF deficiencies "via 1980s facsimile technology" rather than through secure e-mail.

From the editors of the Gold Sheet.
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Loxo Sees Larotrectinib As Model Form Of Oncology Drug Development

MARY JO LAFFLER maryjo.laffler@informa.com

Delivering on the promise of precision medicine, **Loxo Oncology Inc.**'s larotrectinib could be the first of a modern form of oncology drug development – facilitated by US FDA's breakthrough designation program.

Larotrectinib is a targeted therapy that selectively inhibits the tropomyosin receptor kinase (TRK) fusion protein and is one of the first attempts at molecularly defined patient identification rather than traditional indications based on cancer location.

Read the full article here

The first actual FDA approval for a molecularly defined cancer that does not specify tumor location recently went to **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* (pembrolizumab), but the indication for microsatellite instability-high or mismatch repair deficient solid tumors was not the first approval for pembrolizumab and was based on retrospectively collected data. *(Also see "Biomarker-Led Claim Is Small Step For Merck's Keytruda, Giant Leap For Cancer Indications" - Pink Sheet, 23 May, 2017.)*

Larotrectinib could be the first novel drug prospectively developed and approved for a tissue-agnostic claim, as well as the first with simultaneous approval in adults and children.

The pivotal dataset of 55 patients, as agreed with FDA, was presented at the American Society of Clinical Oncology annual meeting June 3 in Chicago.

Lead investigator David Hyman, Memorial Sloan Kettering, described it as "a very efficient and focused development program" that is on "a very rapid path" from discovery to approval. Loxo intends to submit larotrectinib for approval late this year or early 2018, after the data go through independent central radiographic review.

The development process has been facilitated by FDA's breakthrough program. The agency, which has signaled its openness to tissue-agnostic claims for years, issued breakthrough therapy designations for the Keytruda claim and well as for larotrectinib and **Ignyta Inc.**'s entrectinib, another TRK-focused program.

> "FDA issued breakthrough designations for the Keytruda claim as well as for larotrectinib and Ignyta's entrectinib, another TRK-focused program.

"For a program like this which is moving so quickly, it's very helpful to be able to get meetings calendared more quickly, get feedback more quickly. I think that's been the largest benefit [from the breakthrough designation]," Loxo Chief Business Officer Jacob Van Naarden said in an interview at ASCO.

The company's efforts have also been facilitated by CEO Joshua Bilenker's background as an oncology reviewer at FDA. "He has the mind of a regulator," Van Naarden commented.

LOOKING AT THE DATA

The TRK fusion mutation occurs in dozens of cancer types across patients' lifespans. According to ASCO, the abnormality occurs in about 0.5%-1% of many common cancers but in greater than 90% of certain rare cancers, such as salivary gland cancer, a form of juvenile breast cancer, and infantile fibrosarcoma. "At this point it is hard to find a cancer type where TRK fusions have not been reported," Hyman told a press briefing on the results.

There were 17 unique tumor types in the pivotal dataset, including common cancers as well as rare forms and pediatric cancers. Patient ages ranged from 4 months to 75 years, and patients had an average of two prior therapies.

Efficacy was seen regardless of tumor type and no one tumor type responded better than another. In the 50 patients with confirmatory response data, there was a 76% response rate. The other five patients were too early in treatment to have confirmatory scans, but Hyman said all five had at least a partial response and remain on study awaiting their confirmatory scans.

Twelve percent had complete responses, and most partial responses exceeded the criteria with deep tumor regression; two patients moved forward to curative surgery and had pathologic complete responses, Hyman reported.

The median time of first response was 1.8 months, but Hyman explained that reflected the time the first scan was obtained. "In the clinic, patients report dramatic improvement of their symptoms within days of beginning therapy," he said.

The responses have been durable, with 79% of responses ongoing 12 months after starting treatment. Of the responders, 93% remain on therapy or had surgery with curative intent.

"More than three out of every four patients responded to therapy. You'd be hard pressed to find a targeted therapy even within a single disease context that has results like this," Hyman said.

Larotrectinib was also an "extremely well tolerated therapy," the investigator stated, with only 13% of patients requiring any

dose modification and no patients discontinuing due to adverse events. The most common adverse events were fatigue (30%), dizziness (28%), and nausea (28%).

TESTING WILL BE CRITICAL

"Not long ago it would have been a pipe dream to think that we could treat cancers independent of their site of origin," City of Hope's Sumanta Kumal Pal said in reaction to the larotrectinib data. While clinicians at major medical centers like Pal might be ready for "the era of treatment based on the patient not location," it won't be an easy transition, especially in community settings.

For all of the tissue-agnostic approaches, awareness and testing are essential to success. FDA approval of next-generation sequencing (NGS) panels should help – **Foundation Medicine Inc.**'s *FoundationOne* and **Thermo Fisher Scientific Inc.**'s *Oncomine* are both under review. *(Also see "Thermo Fisher Makes Final Push For 'Universal' Lung-Cancer Companion Dx" - Medtech Insight, 14 Nov, 2016.)*

Currently, limited testing makes it hard to be certain of population estimates, Van Naarden acknowledged. Loxo's commercial efforts will focus on diagnosis and awareness. It is also working on a companion diagnostic with **Roche**'s **Ventana Medical Systems Inc.**, an immunohistochemistry test that will come in at a lower price point than the NGS panels.

Pal also pointed out that it will be important to understand how to use larotrectinib in patients with tumor types that have a well-stocked armamentarium, although the drug will be easily adopted in rare cancers with no established standard of care. The same holds true for Keytruda, he noted. "With these mounting data there seem to be increasing calls to obtain molecular profiling in a wide variety of scenarios," Pal said. "It will be important to develop guidelines around testing for these expanding indications."

Physician use will be guided by FDA's labeling, which Van Naarden predicted would "be somewhat flexible … and allow clinicians to make clinical judgement decisions." The breakthrough designations specify use in locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies.

FDA will probably find additional data to be necessary, but that's another area where Van Naarden expects the agency to be flexible if accelerated approval is granted. "There's a lot of ways to build data packages in this modern era," he said, and the agency has expressed desire to see more real-world evidence.

Loxo is also running a clinical program for a follow-on TRK inhibitor, LOXO-195, which is intended as a therapeutic option for patients who develop resistance to larotrectinib. Van Naarden explained that research indicates that tumors can acquire point mutations in the TRK fusions that would prevent larotractinib from binding where it had been, but that the tumor would still be addicted to the same pathway and a new TRK inhibitor that binds differently would be effective. "The idea behind LOXO-195 is this sequential therapy extension of durable disease control," Van Naarden said, akin to EGFR inhibitors in lung cancer.

LOXO-195 is being studied in patients who progress on larotrectinib, and it worked in the first two patients that developed resistance. "Eventually patients will need it – we don't know when and hope it's a long time – but we want it to be there when they do," the exec said. It was a very deliberate effort, he noted, "and frankly we think this is how modern oncology drug development ought to happen."

NOT A UNIVERSAL MODEL

While NGS diagnostics will facilitate treatment based on molecular signature and help deliver on the promise of the genomics revolution, the histology-independent model is unlikely to revolutionize oncology drug development.

In recent years, industry and non-industry groups have embraced "basket" trial designs driven by biomarkers, like **Novartis AG**'s SIGNATURE trial, ASCO's ongoing TAPUR trial and the NCI-MATCH trial from the National Institutes of Health. *(Also see "Genomics-Driven Trials Built To Be Fast And Flexible" - Pink Sheet, 21 Sep, 2015.)*

But some of the early basket trials to report have suggested tumor histology cannot be ignored.

Roche's VE-BASKET trial of *Zelboraf* (vemurafenib), a Phase II trial in patients with any type of nonmelanoma cancer who had BRAF V600 mutations, found that histologic context still mattered. Hyman was also lead author on VE-BASKET, and concluded in the New England Journal of Medicine that "an important implication" of the trial was that conventional treatment based on organ site, with molecular subtypes, "cannot be entirely replaced by molecular nosology (e.g. BRAF-mutated cancers)." *(Also see "Tissue-Agnostic Approach To Cancer Drug Development Takes A Hit" - Pink Sheet, 14 Sep, 2015.)*

Puma Biotechnology Inc. similarly found in its SUMMIT study of neratinib, also led by Hyman and presented at the American Association for Cancer Research annual meeting this April, that the drug had activity in some types of cancer with HER2-activating mutations but not others. *(Also see "Puma's Neratinib SUMMIT Study Shows Potential & Pitfalls Of Precision Medicine" - Pink Sheet, 2 Apr, 2017.)*

Probably the most likely application of tissue-agnostic drug development will be as a way to identify treatment for rare cancers.

Identification of targets is also easier said than done, but the increased information to come from greater use of less-expensive NGS will offer data mining opportunities. For example, TRK fusions were first discovered in 1982 but only gained practical attention with the development of next-generation sequencing.

But this sort of development poses a chicken-or-the-egg problem – does the detection of the mutation come first, or does the therapeutic that can target the mutation? "This is a real advance that we're seeing here today because it shows that it's important to look for it, because you have a treatment that could work for it," John Heymach, MD Anderson Cancer Center, pointed out during a discussion of the larotrectinib results.

"You only find what you look for," Heymach said.

Loxo's Van Naarden had a similar take. "You have to run the clinical trial and look," he said. "You really don't know a priori."

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Advocacy Groups See Sunscreen Risks Where Industry Sees Efficacy

RYAN NELSON ryan.nelson@informa.com

The Environmental Working Group continues to rank mineral-based sunscreens more highly in its annual Guide to Sunscreens due to what it considers chemical filter risks, and concerns about oxybenzone, specifically, but that industry dismisses.

"Most non-mineral sunscreens score poorly in EWG's sunscreen guide because they include potentially toxic additives, including oxybenzone, an endocrine-disrupting chemical, or retinyl palmitate, an antioxidant additive that might damage sun-exposed skin," the group explains in the "Imperfect Protection" section of its 2017 sunscreen report.

According to EWG, few if any particles of zinc oxide and/or titanium dioxide in mineral sunscreens penetrate skin, making them generally safer choices for sun protection than chemical-based options, it suggests.

However, active ingredient particles in mineral formulas tend to be nano-sized, which can pose risks if they aren't coated with inert chemicals to reduce photoactivity, EWG says.

Complicating matters further, the group notes Consumer Reports research suggesting mineral sunscreens, compared with their chemical counterparts, are less likely to provide the level of SPF protection stated on labels.

In CR's 2016 report, just 39% of mineral sunscreens it tested were found to have SPFs consistent with labeled claims (75% or greater than claims), compared to 69% of non-mineral sunscreens.

On average, mineral and non-mineral sunscreens tested at 64% and 86% of claimed SPF values, according to EWG's summary of CR data.

Just as the Personal Care Products Council has suggested, EWG says CR employs "a slightly different [SPF testing] method than the FDA mandates for sunscreen companies," adding, "The reasons for the discrepancy between Consumer Reports and manufacturer's reported SPF values are unclear."

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Much of advocacy groups' messaging on sunscreen products may be clouding the picture for consumers, not least of all EWG's assertion of "very little evidence that sunscreen prevents most types of skin cancer."

Much of the messaging coming from consumer health and environmental advocacy groups regarding sunscreen products may be clouding the picture, not least of all EWG's assertion that "most scientists and public health agencies – including the Food and Drug Administration itself – have found very little evidence that sunscreen prevents most types of skin cancer."

While FDA has noted in its communications that no clinical study has shown sunscreen use alone can prevent skin cancer, it allows marketers of sufficiently protective, broad-spectrum sunscreens to claim their products reduce skin-cancer risk when used in combination with other sun-protection measures. *(Also see "EWG Report Smears Most Sunscreens, Questions Cancer Prevention Efficacy" - Pink Sheet, 1 Jun, 2015.)*

Again this year, PCPC pans EWG's skin cancer commentary, saying it is "not just false – it is irresponsible."

"Sun protection and sunscreen use are critical to preventing skin cancer and premature skin aging," the trade group maintains. "According to the Skin Cancer Foundation, approximately 90% of non-melanoma skin cancers and 86% of melanomas are associated with exposure to UV radiation. Daily use of an SPF 15 or higher reduces the risk of developing melanoma by 50%."

PCPC also continues to reject EWG concerns about oxybenzone. It says the UV filter that EWG claims is a potential endocrine disruptor and sensitizer is "unjustly criticized every year."

Chief Scientist Beth Jonas points out in PCPC's May 23 statement that oxybenzone is one of the few FDA-approved ingredients that provides effective protection against a wide range of UVB and UVA rays, and its safety is backed by the American Academy of Dermatology, available peer-reviewed scientific literature and regulatory assessments from national and international bodies around the world.

Education and expert guidance clearly is important amid mixed messages from advocacy groups and obvious consumer confusion, based on reader comments posted to CR's website.

Consumers there seem to question their options in light of CR's general recommendation to seek out chemical sunscreens and the prevailing sentiment that anything "chemical" is dangerous.

Sunscreen marketers clearly have their work cut out of them in terms of countering misinformation, combating chemophobia and reassuring consumers so that sunscreen use, as PCPC phrases it, is "as much of a habit as using your seatbelt."

From the editors of the Tan Sheet.
Published online June 1, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Novo Nordisk's *Victoza* (liraglutide) as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse CV events in adults with type 2 diabetes and high CV risk	Endocrinologic and Metabolic Drugs	June 20
Potential pediatric development plans for Apexigen's APX-005M, PharmaMar USA Inc.'s PMO1183 (lurbinectedin) and Astellas Pharma Global Development's ASP2215 (gilteritinib)	Pediatric Oncology Subcommittee	June 21
Potential pediatric development plans for Dista Products/Eli Lilly's prexasertib and Lilly's olaratumab	Pediatric Oncology Subcommittee	June 22
FDA biotechnology activities related to plant-derived food and animals and report from the National Antibiotic Resistance Monitoring System Review Subcommittee	Science Board	June 26
Pfizer's *Mylotarg* (gemtuzumab ozogamicin) in combination therapy with daunorubicin and cytarabine for the treatment of adults with previously untreated, de novo acute myeloid leukemia	Oncologic Drugs	July 11
Novartis' tisagenlecleucel-T suspension for treatment of pediatric and young adults ages 3-25 years with relapsed/refractory B-cell acute lymphoblastic leukemia	Oncologic Drugs	July 12
Amgen's ABP 215, a proposed biosimilar to Genentech/Roche's *Avastin* (bevacizumab)	Oncologic Drugs	July 13 (morning)
Mylan's MYL-1401O, a proposed biosimilar to Genentech's *Herceptin* (trastuzumab)	Oncologic Drugs	July 13 (afternoon)
Safety and efficacy of Dynavax's hepatitis B vaccine	Vaccines and Related Biological Products	July 28

Pink Sheet

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52 Vanderbilt Avenue, 11th Floor
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