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Half Of All EU Fast-Track Requests Fail; AZ's Imfinzi Among Latest

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Companies hoping to fast-track their products in Europe have about a 50/50 chance of getting on the accelerated assessment program at the European Medicines Agency.

In the year to date, the EMA's Committee for Medicinal Products for Human Use has assessed pre-filing accelerated access requests relating to ten products. Five have been granted and four, if not five, have been refused – including recently for AstraZeneca's PD-L1 blocker, *Imfinzi* (durvalumab), in Stage III non-small cell lung cancer. The result of the tenth request is unknown but it may well have been refused. Three of the five requests granted relate to products with orphan status. A fourth had orphan status but no longer does.

The Imfinzi refusal is a disappointment for AstraZeneca, which is keen to get the product approved as soon as it can for use in patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy. *(Also see "No EU Fast Track for AZ's Imfinzi In Stage III Lung Cancer" - Pink Sheet, 5 Oct, 2017.)* This is the second accelerated access request relating to Imfinzi that the CHMP has turned down. A request relating to the advanced bladder cancer indication – for which the product was approved in the US in May – was rejected at the end of last year.

AstraZeneca filed for marketing approval of Imfinzi with the EMA in the NSCLC indication in the past month. The company has high hopes for the product in general but this earlier-stage NSCLC indication is of particular interest.

CUTTING REVIEW TIMES

Accelerated assessment can cut the time it takes the CHMP to review a marketing authorization application (MAA) under the centralized procedure from 210 days (not counting clock stops when applicants have to provide additional information) to 150 days. Products granted speedy review must be of major interest for public health or show therapeutic innovation. According to the EMA, three quarters of the MAAs initiated under the fast-track mechanism were completed under the accelerated timetable during the first half of 2017.

The EMA advises companies to submit their requests for accelerated assessment two to three months before they submit their MAA.

FIVE YES, FOUR NO, ONE NOT SAYING

The CHMP has agreed to requests for accelerated assessment this year to date for the following products:

- **Merck Sharp & Dohme Ltd.**'s letermovir, for prophylaxis of cytomegalovirus infection or disease in adult CMV

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Merck Calls It Quits On Anacetrapib
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Despite success in REVEAL outcomes trial, Merck will not submit the for the cholesteryl ester transfer protein (CETP) inhibitor for regulatory approval.

Aerie's Netarsudil's Safety Questions May Determine Fate At Advisory Committee
https://pink.pharmamedtechbi.com/PS121744
Proposed treatment for elevated intraocular pressure would be first in new rho-associated protein kinase inhibitor class.

What EU Governments Need To Do About Access To Affordable Medicines
https://pink.pharmamedtechbi.com/PS121742
In a wide-ranging discussion at the recent European Health Forum Gastein, policy makers explored big-picture challenges and ideas of what governments should do to ensure access to increasingly expensive medicines as pressures grow on national health care systems.

NIH/Industry Oncology Partnership Aims For Immunotherapy Biomarkers
https://pink.pharmamedtechbi.com/PS121755
Part of the Cancer Moonshot program, the five-year, $215 million research collaboration will be mostly funded by NIH with money from the 21st Century Cures Act.

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seropositive recipients of an allogeneic hematopoietic stem cell transplant (granted in March). *(Also see "New Anti-CMV Therapies Post-Transplant: Merck & Co Leads The Pack" - Pink Sheet, 2 Mar, 2017.)*

- Dr. Falk Pharma GMBH's budesonide for the treatment of active eosinophilic esophagitis in adults (April).
- **Roche**'s emicizumab for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) who have factor VIII inhibitors (May).
- **Kite Pharma Inc.**'s CAR-T therapy, axicabtagene ciloleucel (KTE-C19), for the treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma, primary mediastinal B cell lymphoma, and transformed follicular lymphoma who are ineligible for autologous stem cell transplant (June).
- **Sanofi**'s fexinidazole, for the treatment of sleeping sickness (September). This product will be evaluated under the Article 58 provision, which is for products for use in developing countries. *(Also see "Sanofi Secures EMA Accelerated Assessment For Sleeping Sickness Drug" - Pink Sheet, 18 Sep, 2017.)*

According to the EMA's newly updated list of products under review, a total of five products are currently being evaluated by the agency under this mechanism. They are letermovir, budesonide, emicizumab, and axicabtagene ciloleucel – all listed above – and glibenclamide, seemingly from AMMTeK France for the treatment of neonatal diabetes.

Other than Roche's emicizumab, all five products under review have orphan status. Emicizumab originally had orphan status but this was withdrawn in May this year at the request of the sponsor.

Fexinidazole, whose accelerated access request was only granted last month, has not yet been filed for marketing authorization.

The following products join Imfinzi in having had their requests for accelerated assessment refused this year:

> "EMA said 57% of accelerated assessment requests were granted and 75% of applications initiated under this mechanism were completed on the accelerated timetable in the first half of 2017.

- **Amgen Inc.** and **Novartis AG**'s *Aimovig* (erenumab), for the prophylaxis of migraine in adults (refused in March). *(Also see "Keeping Track Of Novel Agents: US FDA Approves Nerlynx And Vosevi, Turns Down Evenity; Macrilen Returns" - Pink Sheet, 23 Jul, 2017.)*
- **Vertex Pharmaceuticals (Europe) Ltd.**'s tezacaftor/ivacaftor combination, an orphan-designated treatment for patients with cystic fibrosis aged 12 years and older who have at least one F508del mutation in the CFTR gene, and a second mutation that is responsive to tezacaftor/ivacaftor (May).
- Buprenorphine, for the treatment of opioid dependence within a framework of medical, social and psychological treatment in adults and adolescents aged 16 years or older (June).
- A request for **Jazz Pharmaceuticals PLC**'s orphan-designated *Vyxeos* (cytarabine, daunorubicin) for acute myeloid leukemia was assessed in September but the outcome is not yet known. *(Also see "Jazz On Track With Q4 EU Filing for Leukemia Treatment Vyxeos" - Pink Sheet, 14 Sep, 2017.)* Jazz told the *Pink Sheet* last week: "We have nothing new to release at this time."

PROCESS

Accelerated review requests are assessed by experts and recommendations on whether they should be granted or refused are put before the CHMP for adoption at the committee's monthly meetings. There is usually a six-week gap between the CHMP making its decision and the EMA disclosing the results. The results are included in the minutes of the CHMP meeting at which the decisions are taken; each CHMP meeting generally adopts the minutes for the previous meeting and the minutes are generally published a week or two after the end of the CHMP meeting where they were approved. Companies may decide to reveal the result themselves before the minutes are published, as was the case with Sanofi's fexinidazole.

ASTRAZENECA

A decision on AstraZeneca PLC's prefiling request that Imfinzi be fast-tracked by the EMA in the Stage III NSCLC indication was taken at the CHMP's July meeting. According to the recently published minutes of the meeting, the request was refused. The *Pink Sheet* approached AstraZeneca for the result shortly after the July meeting but got no response. The CHMP gives no reasons for such refusals; AstraZeneca said "the discussions on 'why not' are confidential". The company has since filed for approval.

Imfinzi received its first approval in May – in the US under the Food and Drug Administration's accelerated approval pathway for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has progressed during or after one standard platinum-based regimen. The CHMP refused AstraZeneca's fast-track request for Imfinzi in the advanced bladder cancer indication at its meeting in December 2016. Unlike in the case of the NSCLC indication, AstraZeneca did not go ahead and submit an MAA for advanced bladder cancer. Announcing its MAA submission for Imfinzi in NSCLC, the company said: "This is the first registrational submission for *Imfinzi* in the European Union."

Imfinzi secured breakthrough therapy designation in the Stage III NSCLC indica-

tion in the US in July. It does not have orphan status in the EU.

AstraZeneca's hopes for Imfinzi in the Stage III NSCLC indication were boosted following the recently announced positive results of the PACIFIC trial. Depending on when Imfinzi reaches the market in this indication, AstraZeneca could be the only player in the earlier-stage lung cancer space for a couple of years. Trials of other anti-PD-1/L1 agents such as **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) are only just beginning.

MID-YEAR REPORT

The EMA recently highlighted the fact that it continued to support early access to medicines for patients through the accelerated assessment framework. It said: "57% of requests for accelerated assessment were granted and 75% of the marketing authorisation applications initiated under this mechanism were completed under the accelerated timetable during the first half of 2017."

The figures are part of the EMA's soon-to-be-published mid-year report, which was adopted by the agency's management board at its meeting last week.

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BIOSIMILARS

Neulasta Is 4-0 Versus Biosimilars Now That Mylan Has A CRL From FDA

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Mylan NV is the fourth company to receive a complete response letter from FDA related to a biosimilar version of Amgen Inc.'s *Neulasta* (pegfilgrastim), highlighting the challenges with bringing a copy of the pegylated neutropenia drug to market.

Mylan and its biosimilar development partner **Biocon Ltd.** announced the CRL Oct. 10 and said it was related to a pending update of the BLA with new Chemistry, Manufacturing and Controls (CMC) data from a facility requalification after the plant was modified.

"The CRL did not raise any questions on biosimilarity, pharmacokinetic/pharmacodynamic data, clinical data or immunogenicity," Mylan and Biocon said in a statement. During Mylan's second quarter sales and earnings call in August, President Rajiv Malik said the company was continuing to work with FDA on good manufacturing practice (GMP) issues.

The company said it does not expect the CRL to impact the potential commercial launch timing of the product in the US, which is targeted for late 2018 or early 2019. Malik previously said Mylan is not forecasting any meaningful revenues from biosimilars in 2018.

The three other manufacturers that have seen their respective Neulasta biosimilar BLAs hung up by FDA include **Sandoz International GMBH**, **Coherus BioSciences Inc.** and **ApotexInc./Intas Pharmaceuticals Ltd**. The four CRLs highlight the challenges with developing a biosimilar version of pegfilgrastim and apparently adding polyethelene glycol to a product. *(Also see "Taking Biosimilars Down A PEG: Why Copying Neulasta Isn't So Easy" - Pink Sheet, 13 Jun, 2017.)*

The reasons for the CRLs have varied, however. Coherus said FDA's letter focused on a request for a reanalysis of a subset of samples from a clinical immunogenicity study with a revised assay. Sandoz didn't elaborate on the details of its CRL, but earlier this year the company withdrew an application for biosimilar Neulasta in Europe after the European Medicine Agency's advisory group said the company did not show similar concentrations of pegfilgrastim in the blood with its product and Neulasta. Apotex has not commented on the CRL it received or even confirmed that it received one, but its product had a user fee date in 2015.

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For now, Amgen remains the winner, since Neulasta generated $2.3bn in the first half of 2017.

The disappointing news could not tamper momentum at Mylan, however, following an announcement Oct. 3 that the company scored the first FDA approval of a generic version of **Teva Pharmaceutical Industries Ltd.**'s 40mg version of *Copaxone* (glatiramer) for multiple sclerosis. *(Also see "Surprise! Mylan's Copaxone Generic Sets Teva Up For A Struggle" - Pink Sheet, 4 Oct, 2017.)* The company launched its 40mg version and a 20mg dose administered daily the next day.

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Cinfa Banks On 'Multi-Layered' Scientific Advice As It Files For EU Pegfilgrastim Biosimilar Review

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Cinfa Biotech sought extensive scientific advice for its biosimilar

> "From the very beginning, we developed a strong rationale of what we were doing and why we were doing it" – Ruediger Jankowsky, Cinfa Biotech

Cinfa Biotech is banking on extensive scientific advice from regulators in the EU to ease the path to approval for its biosimilar version of Amgen's blockbuster drug Neulasta (pegfilgrastim) for treating chemotherapy-induced neutropenia.

The Spanish company filed a marketing authorization application (MAA) for its lead product candidate, B12019, with the European Medicines Agency last month. Cinfa Biotech is attempting to break into a segment of the biosimilars market that has so far eluded its competitors.

Biosimilar pegfilgrastim is notoriously difficult to develop. While marketing applications for such a product have been reviewed by regulators in the past, none of them have made the grade, neither in the EU or the US.

B12019 was developed using a "highly efficient development approach," Cinfa Biotech's managing director, Ruediger Jankowsky, told the *Pink Sheet*. The product's development was completed in just four years.

According to Jankowsky, efficiency was achieved largely as a result of the "multi-layered" approach the company took to obtaining scientific advice. This approach helped the company reflect as much as possible "the current scientific and regulatory thinking in the development of our product," he explained. It also helped the company avoid carrying out "large and insensitive clinical trials."

"From the very beginning, we developed a strong rationale of what we were doing and why we were doing it," Jankowsky said. One of the key questions for the company was "what is the appropriate clinical development program."

The Cinfa Biotech executive explained that clinical studies as carried out in the biosimilars space are often not sensitive when it comes to detecting any differences between the biosimilar and its reference product. These studies are often large and costly. "Cinfa Biotech therefore tailored the clinical studies of B12019 to the specific properties of pegfilgrastim to allow for the sensitive detection of differences between the biosimilar and the reference product," he said.

"After deciding on the most reasonable approach for detecting any differences [between B12019 and Neulasta], we developed a very straightforward clinical development strategy that we immediately started discussing with regulatory authorities," Jankowsky said.

"We sought scientific advice not only from the EMA, but we also spoke to a number of European national competent authorities that have experience with biosimilars such as those in Germany, Finland, Austria and Spain. We discussed our development program with them from the very beginning in order to obtain feedback and learn about their expectations and any questions they might have."

These discussions, Jankowsky said, were a positive experience. "We found that if you can provide a strong rationale to the authorities, they are open to discussing it – and accepting it if it is convincing and justifiable."

B12019 is one of three biosimilar pegfilgrastim products currently under review at the EMA as of Oct. 4. Coherus BioSciences has previously indicated that it is one of the three applicants. The remaining applicant does not appear to have gone public.

Several companies have failed in their attempts to bring a biosimilar pegfilgrastim to the market. Novartis/Sandoz and Gedeon Richter withdrew their EU applications after the EMA's human medicines evaluation committee, the CHMP, said that their study data was not good enough. Mylan/

Biocon withdrew theirs against a backdrop of manufacturing compliance lapses at Biocon's Indian site. In the US, the Food and Drug Administration has rejected marketing applications from Coherus, Apotex/Intas Pharmaceuticals, and Sandoz.

A LOT OF COMPLEXITY

The development of pegfilgrastim, which is the pegylated form of filgrastim, is very complex. It is this pegylation that introduces complexity in the molecule, Jankowsky explained, adding that pegylation leads to problems such as increased variability when it comes to the molecule's pharmacokinetics.

Cinfa Biotech's EU MAA for B12019 was supported by biosimilarity data from analytical, biofunctional and clinical studies comparing the biosimilar with Neulasta. Based on scientific advice from the EMA, the clinical development program included two studies that confirmed the analytical and biofunctional similarity of B12019 and Neulasta "in highly sensitive clinical study settings," the company said.

In May, the company announced positive top-line data from the second clinical study. The multiple-dose, randomized, double-blind, three-period cross-over study enrolled 96 healthy volunteers in Germany. It demonstrated comparability of B12019 and Neulasta with regard to pharmacodynamics and immunogenicity. All primary and secondary study endpoints were met.

PLANS FOR THE US MARKET

Cinfa Biotech, which is headquartered in Pamplona, Spain, with offices in Munich, Germany, also has its eye on the US. The company is planning to explore entering that market in the future, but for now it is focusing on the EU market.

The company, which is the biosimilars arm of the Cinfa Group, is creating a pipeline of biosimilar drugs for a range of indications. "We have started a second project but we are not yet disclosing the identity of the product for confidentiality reasons," Jankowsky said. "The plan is to build in the future a strong and robust pipeline of high-quality biosimilars," he said, adding that the company was exploring inflammatory diseases as well as oncology.

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Real-World Evidence: Advice, Principles And Examples Emerge From FDA

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US FDA officials appear most comfortable applying "real-world evidence" to the challenges of patient selection for clinical trials – rather than jumping ahead to using those data sources as a basis for a drug approval decision.

During a week of workshops focused on the theme of real-world evidence in mid-September, FDA officials repeatedly made the point that the agency can, does and will use real-world evidence to support regulatory decision making – but not that it will tie drug approval decisions directly to applications built on real-world data.

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Instead, FDA officials suggested ideas like using data from health systems electronic records and claims to help identify populations for more effective Alzheimer's Disease clinical trials. That specific suggestion came from Center for Drug Evaluation & Research Deputy Director Robert Temple, speaking from the audience during a Sept. 13 public workshop on creating a Regulatory Framework for the Use of Real World Evidence put on by Duke-Margolis under a cooperative agreement with FDA.

Temple suggested that real world data might provide a way to define an at-risk population before they "are overtly sick" and thus permit sponsors to work with endpoints to show impact on progression in a short-term (two- or three-year) period.

"The endpoints," Temple said, could "be an early diagnosis of mental dysfunction or next stage" of disease. That seems "sort of promising," Temple said, "because those are things that are picked up in the system" of real-world data.

Temple's comments at meetings like the Duke-Margolis workshop may appear as ruminations or digressions from the main topic. However, given the ongoing work to draft guidance on applications of real-world evidence (RWE), it is hard not to interpret them as a guidepost to the agency's thinking at this point.

In this case, using the multiple-failure clinical trial area around Alzheimer's as enticement, Temple suggests that an appropriate use of real-world evidence is to

improve the design and potential for success from clinical trials.

That's a step back from the firm commitment that many in industry have been seeking that FDA will accept real-world data as evidence for regulatory decisions on certain types of submissions, such as supplemental and post-marketing applications.

However, Temple is defining one of the safe functional uses for real-world data at this point, and presumably identifying one idea that may be incorporated into the guidance that FDA is working on as part of its commitments under the PDUFA VI agreement and in response to the directives of the 21st Century Cures Act.

A statement on the value of RWE to support endpoint development and tailor populations for shorter clinical trial trials would be akin to the general advice sections of some of FDA's drug guidances like the first part of the recent January guidance on "Multiple Endpoints in Clinical Trials."

The RWE effort has the clear support of FDA Commissioner Scott Gottlieb. He told one of the recent workshops that "We're now working on policies to support the use of RWE in the approval of new indications for already marketed drugs. This may be especially relevant in settings like rare diseases or other unmet medical needs, where it can be hard to enroll patients in clinical trials."

Two of the three September workshops were held by the Duke-Margolis Center and one by the National Academies of Science, Engineering and Medicine. All three were in conjunction with FDA and are part of the ongoing effort to move FDA and the regulated industry to a better understanding and regulatory framework for more widely incorporating real world data and evidence into regulatory applications.

Gottlieb declared the agency's current view that it can accept real-world evidence at its discretion in a keynote address to the Sept. 19 NASEM meeting. "Make no mistake," Gottlieb said, "there's nothing in our statute or regulations that prevent FDA from using a broad range of informative sources of evidence."

> "We're now working on policies to support the use of RWE in the approval of new indications for already marketed drugs." – Commissioner Gottlieb

FDA Principal Deputy Commissioner Rachel Sherman struck that same theme later at the workshop. She pointed out at the that neither the drug or device standards for approval "talk about where or how one collects the information, data, or evidence."

Center for Drug Evaluation & Research Director Janet Woodcock was more specific about the types of projects where FDA has already accepted real world-evidence. Like Temple's advice on patient selection, these situations are likely to be reflected in the upcoming guidance.

Read the full article here

From the current hints from FDA, the guidance looks like it will incorporate advice, principles (randomization and pre-specification of endpoints and analysis add reliability) and examples.

Here are two examples offered by Woodcock:

How to incorporate registry data into support for a new indication: Woodcock's example of recent FDA activity in this area is the May 17 extended indication (from 10 cystic fibrosis mutations to 33) for the Vertex product, *Kalydeco* (ivacaftor), based on registry data with mechanistic information from lab studies and trial data. *(Also see "Kalydeco Expands Indication Without Clinical Data; Keytruda Is Latest Bladder Cancer Approval" - Pink Sheet, 21 May, 2017.)*

Woodcock described her active involvement in the agency's decision to use a combination of registry data, mechanistic lab studies and trial data.

"I asked the Cystic Fibrosis Foundation to look" at their "very good" registry for data on FEV1 readings before ivacaftor treatment and after, Woodcock recounted. "They found that they had a sustained increase in FEV1 after switching over to ivacaftor. Subsequently we were able to use mechanistic data along with some trial data to add those mutations to the indication."

The CDER director projected this experience to other diseases. "You could see in the future that you could use this [approach] to indications to different diseases especially as we're approving sort of mutation-by-mutation in these targeted therapies." She specifically cited the relevance to oncology.

Creating an environment for merging clinical trials with treatment ("platform trials"): Woodcock continues to push for more sponsors to participate in multi-product trials run under master protocols – "continuous ongoing trials rather than start-and-stop trials and they can study many things" such as biomarkers, devices, and outcomes in a disease. *(Also see "Master Protocols Are Both Welcome And Inevitable – US FDA's Woodcock" - Pink Sheet, 6 Jul, 2017.)*

Woodcock described these trials, which have to this point "been run by consortia that have experienced trialists as principal investigators," as a source for evidence generation from which FDA would feel more comfortable accepting a range of data. Woodcock explains how these trial environments could effectively merge treatment (aka real-world) data with clinical trials.

"I think the most important thing here is that because they are continuous rather than start-and-stop, they could add elements to incorporate data collection and trial procedures into the care process," Woodcock said. That would give data generated from these trials "the characteristics of real-world evidence but continue randomization and certain other things that are necessary … for studying new products."

From the editors of the RPM Report.
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US FDA's Top Tips For Tumor Agnostic Drug Development

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The US FDA is advising sponsors to carefully consider the appropriateness for developing drugs across tumor types and to work collaboratively on biomarkers in the wake of the groundbreaking approval of **Merck & Co. Inc.**'s *Keytruda* for a "tissue-agnostic" indication.

Merck's PD-1 inhibitor Keytruda (pembrolizumab) won accelerated approval in May for any type of solid tumor that are microsatellite-high (MSI-H) or mismatch repair deficient (dMMR), marking the first clearance based solely on a biomarker, without being guided by tumor location. Approval was supported by data across five multicenter single-arm studies of 149 patients with MSI-H or dMMR tumors. In these trials, the objective response rate was 39.6%, with responses lasing six months or more in 78% of responders. Of the responses, 11 were complete and 48 were partial.

FDA's Oncology Center of Excellence Director Richard Pazdur and colleagues at the agency reflect on the Keytruda approval and share their thinking on how other sponsors could pursue tissue-agnostic approvals and in an Oct. 12 perspective piece in the *New England Journal of Medicine*.

The pembrolizumab approval marked a departure from the past in that it "allowed extrapolation of the observed treatment effect to diverse tumors," Pazdur and fellow FDA officials Steven Lemery and Patricia Keegan wrote in the NEJM article.

As a follow-up to accelerated approval of pembrolizumab in MSI-high or dMMR tumors, FDA asked Merck to run additional non-randomized studies evaluating response rate and duration of response.

"Most accelerated approvals require sponsors to perform randomized trials after approval; however, given the limited number of patients and the unprecedented effects on response rate and response duration in diseases such as MSI-H or dMMR endometrial cancer, biliary cancer, or pancreatic cancer, randomized trials were not believed to be feasible," the article noted.

One shortcoming of the Keytruda approval was the "lack of an FDA-approved test to identify patients with MSI-H or dMMR cancers," the FDA officials wrote.

"Although not FDA-approved, testing for MSI-H or dMMR as a prognostic determinant for colorectal cancer recurrence has been available for decades in medical practice. The FDA approved this indication without approved companion diagnostic tests for MSI-H or dMMR because of the high unmet medical need (with most patients having few therapeutic options), the high response rate, and the known safety profile," the officials explained.

"Merck committed to developing tests for MSI-H and dMMR after approval," they added.

In the article, titled "First FDA Approval Agnostic of Cancer Site – When a Biomarker Defines the Indication," the FDAers advised sponsors to "carefully consider whether any development program they pursue is appropriate with respect to the given indication."

In designing trials, they should look a range of factors including available therapies, unmet need, the magnitude of benefit and the size of the patient population.

> "Sponsors should carefully consider whether any development program they pursue is appropriate with respect to the given indication," FDA officials advise.

"Single-group trials may be useful when no therapies are available for a patient population, when initial response rates to the investigational drug are markedly superior to those of available drugs, or when small patient numbers may preclude an adequately designed randomized trial," the article states.

The FDA officials noted the low incidence of MSI-H or dMMR in most tumor types. For most types, the incidence is 5%, though it is more common in certain cancers, such as endometrial (almost 30%) and colon or gastric cancer (20%).

These figures derive mostly from primary tumor specimens and the prevalence in metastatic cancer is "expected to be low for most tumor types, especially for rare cancers such as cholangiocarcinoma or small-bowel cancer," the authors noted.

Furthermore, the "favorable prognosis associated with dMMR in early-stage or localized colorectal cancer does not appear to be maintained in patients with metastatic disease," the officials said.

Certain biomarkers may not lend themselves to this drug development strategy, the article advised. For example, BRAF/MEK and HER2 are useful biomarkers for some tumor types but not others.

> One shortcoming of the Keytruda approval was the "lack of an FDA-approved test to identify patients with MSI-H or dMMR cancers."

Results from the molecularly-targeted National Institutes of Health NCI-MATCH study and the American Society of Clinical Oncology's Targeted Agent and Profiling Utilization Registry (TAPUR) study, both of which are now enrolling, could help inform sponsors drug development in this space in the future.

FDA STRESSES COLLABORATIVE APPROACH

"Although sponsors have conventionally focused on the development of a drug, the strategy of pursuing site-agnostic indications must focus on both drug and biomarker development," the article states.

A number of commercial sponsors may be developing drugs for a particular biomarker-defined indication and should work together to develop new biomarkers, such as tumor mutation burden as a predictor of response to immunotherapy.

"If a biomarker will, in essence, define the disease indication, then it should be developed through the collaboration of multiple stakeholders including commercial sponsors, device manufacturers, academia, and patient," the officials said.

Read the full article here

FDA's acceptance of the tissue-agnostic approach will be tested by a pair of similar candidates. Both **Loxo Oncology Inc.**'s larotrectinib (LOXO-101) and **Ignyta Inc.**'s entrectinib are in late-stage development for NTRK fusion-positive, 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. The two programs each have breakthrough designations and are expected to file in the next year.

Loxo made a big splash with the initial data for larotrectinib at ASCO in June, and the firm thinks it will have the first novel drug prospectively developed and approved for a tissue-agnostic claim. *(Also see "Loxo Sees Larotrectinib As Model Form Of Oncology Drug Development" - Pink Sheet, 5 Jun, 2017.)*

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China Innovation Policy Reform Streamlines Trial Management

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Alarmed by the drug lag of five to seven years compared to the US, Europe and Japan, Chinese drug regulators have put forth a string of policy initiatives to tackle it. The latest effort is also perhaps the most ambitious one thus far.

On Oct. 8, China's Cabinet, the State Council released Opinions on Deepening Regulatory Reforms to Encourage Drug and Medical Device Innovation, finalizing earlier proposals and outlining measures to further stimulate the development of innovative new drug and medical devices. However, since few details are provided so far, implementation will be key to understanding how these potentially significant changes work in practice.

The first task outlined by the document is to reform and simplify the nation's current clinical trials site certification process. Even though there are over 10,000 hospitals and clinics in China and roughly 2,000

> China's latest innovation initiative replaces clinical trial site pre-certification with registration and creates provisions allowing use of foreign data.

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are classified as top Class 3 facilities, only 600 have managed to get certified to conduct early-stage Phase I clinical trials.

And the wait for an investigative new drug (IND) and clinical trials approval (CTA) in China is so lengthy that many sponsors choose to conduct such studies in other countries.

Now, qualified sites will be able to conduct trials without getting certified, on the condition that they are registered with the China FDA's designated website, have conducted a minimum of three trials in the past, and have a senior level primary investigator.

CFDA also offers some new flexibility to use clinical data developed outside China for product applications."The data obtained from multiregional studies outside China can be used towards a product registration if they follow the registration requirement. If it's the first time for a sponsor to apply for a registration in China, the sponsor should submit study results demonstrating ethnic differences," noted the document [Opinions on Deepening Regulatory Reforms to Encourage Drugs and Medical Device Innovation: Chinese language].

Equally notable are new pre-set timeframes for IND or CTA approvals, although exact details are unclear. The CFDA said that study sponsors can start a study if the CFDA doesn't object or raise concerns to a proposal by a certain time. The timeframe appears to be either 30 or 60 days.

IPR PROTECTION

The latest document also aims to enhance protection of intellectual property rights. While again exact details are yet to be seen, CFDA outlines methods to protect clinical data, and offers patent linkage and patent extension for novel drugs that encounter lengthy delay during the approval process.

Per the document, sponsors can apply for clinical data protection along with an NDA, and during the protection period, applications for products of the same class from others won't be accepted.

One new initiative is a pilot program to grant compensatory patent term extension to selected new drugs under defined conditions.

The strengthening of IP protection is intended not only to stimulate innovation, but also to promote generics, biosimilars and follow-on drug-device combo products, CFDA officials say.

"The combination of patent linkage, extension and data protection improvement shows concerted efforts to protect IPR," noted CFDA deputy commissioner Wu Zhen in a Oct.9 press briefing. "It's aimed to establish scientific and systematic IPR protection, and by protecting the rights of patent holders, we encourage innovation, as well as generic drugs," Wu added.

The mechanism will protect novel drugs via patent protection and market exclusivity, and after the patent expiry, the launch of generics will allow the prices to fall sharply, Wu said.

CONDITIONAL APPROVALS

China FDA will grant conditional approval to rare disease treatments and treatment of diseases with significant clinical needs, noted the document.

Also, a rare disease catalogue will be issued by the National Health and Family Planning Commission, along with a registry for patients of rare diseases in China.

Sponsors of rare disease treatments can apply to reduce or waive clinical studies. For rare disease treatments already approved outside China, the CFDA can grant conditional approvals, on the condition that sponsors provide post-market surveillance study plans and then conduct such studies.

Other measures include:

1. Establishing China's Orange Book listing all approved drug products;
2. Encouraging generics, biosimilars, and follow-on drug-device combo products to improve market access and reduce economic burden;
3. Rolling out the Marketing Authorization Holder (MAH) system nationwide. MAH holders will be held responsible for pre-and post-market compliance requirements and medical sales representatives registrations;
4. Enhancing the technical review infrastructure for marketing applications. The document calls for a multi-disciplinary technical review system. To increase transparency and oversight, technical review conclusions other than business secrets will be made public. Pre-NDA filling consultations will be arranged to increase communications and guidance.

The document will bolster the pharma industry in China, although the focus remains on implementation as few details are disclosed, observers say.

"The final policy seems to have intentionally left these details out for further elaboration in the implementation measures to be issued by the CFDA and other related government agencies, i.e. the State IP Office," said a legal expert.

From the editors of PharmAsia News.
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Opioids And Psychic Pain: Alkermes Uses High-Profile Stage To Highlight Depression Drug

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Alkermes PLC was a perfectly logical company to include on a roster of presenters during the third meeting of the President's Commission on Combating Drug Addiction and the Opioid Crisis on Sept. 27.

The biopharma industry was the focus of the session, with an emphasis on ideas to advance development of non-addictive pain therapies and new therapies to treat addiction. The meeting kicked off with remarks form National Institutes of Health Director Francis Collins and Pharmaceutical Research & Manufacturers of America CEO Stephen Ubl, and then included testimony from 10 executives from companies engaged in anti-addiction and non-opioid pain research.

As Alkermes CEO Richard Pops wryly noted when his time to present began, "our company has been on the front lines" of developing anti-addiction therapies and "we have all the scars to show for it." Alkermes developed the injectable naltrexone formulation *Vivitrol*, and Pops devoted half his remarks to outlining the issues that can impede use of that therapy – and anti-addiction therapies in general.

His remarks echoed those of other industry presenters, including stressing the need to assure insurance coverage is readily available for medication-assisted treatment – and that the legal directive of the 21st Century Cures Act that all medication-assisted treatment (MAT) providers need to offer access to any approved therapy be fully implemented.

Pops devoted the second half of his remarks to showcasing a near-term potential new therapy. That, too, was in keeping with other presenters from companies like **Indivior PLC**, **Braeburn Pharmaceuticals Inc.** and **US WorldMeds LLC**, who made sure to mention that they have new therapies pending at FDA. (Indivior and Braeburn have separate applications for injectable forms of buprenorphine; US WorldMeds has a potential new treatment for withdrawal symptoms, lofexidine.)

Pops, however, wasn't showcasing a new anti-addiction treatment. Instead, he highlighted Alkeremes submission of a new drug (ALKS 5461) for major depressive disorder.

Pops framed depression as an issue "at the core of both addiction and pain," specifically describing depression as "psychic pain" that often prompts people to experiment with opioids for relief.

His remarks no doubt offer a preview of one argument Alkermes will use to try to secure FDA approval of ALKS 5461. The NDA is supported by only one successful study – though buttressed by two other trials that failed on the primary endpoint but which Alkermes argues provide supportive evidence. *(Also see "If Alkermes Antidepressant Can Get Past FDA, The Market Might Be There" - Scrip, 23 Oct, 2016.)*

The company has already publicly made the case that ALKS 5461 can meet an important unmet need in depression based on its novel mechanism of action and millions of diagnosed patients with inadequate responses to available therapy. If the drug can also be positioned as potentially helpful in the opioid epidemic, that could help assure maximum flexibility from FDA in considering the efficacy data.

FDA may or may not respond to that argument, but Pops' message resonated with the Presidential Commission. Patrick Kennedy (formerly a Democratic Representative from Rhode Island) thanked Pops for raising the issue "psychic pain" and agreed that "we have a combined issue here" in addressing barriers to addiction treatment and to effective treatment for depression. Florida Attorney General Pam Bondi also specifically thanked Pops "for the product that you are developing," noting that "our suicide rate in Florida is through the roof."

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White House Opioid Commission: Access To Drug Therapy, Coverage 'Parity' Urged
http://bit.ly/2gAowqH

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There's The Bolus! ANDA Sponsors Race To Avoid User Fee Spike

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The anticipated bolus of ANDAs from sponsors wanting to avoid a substantial increase in user fees waited until September to manifest. But it arrived nonetheless, and will likely complicate FDA's workload for the coming year.

FDA reported receiving 202 ANDAs in September, the last month of fiscal year 2017. It was the second-highest monthly total for the year and pushed the annual submission tally to 1,292, which was the second-highest in the generic drug user fee program's first five-year cycle.

The cost difference between submitting an ANDA in September versus submitting in October was substantial. ANDA application fees increased 144% to $171,823 on Oct. 1, the first year of GDUFA II. As part of the new user fee cycle, a program fee also was instituted based on the number of ANDAs a firm owned. *(Also see "Generic User Fee Hikes Could Disrupt US FDA Drug Pricing Campaign" - Pink Sheet, 28 Aug, 2017.)*

Generic drug firms' margins can be thin, so the prospect of saving $101,000 if an ANDA is submitted before the new fiscal year begins likely is enough to entice sponsors to try to speed up their timelines. "I am certain that many more ANDAs would have been submitted if the industry had an earlier warning on the increase in ANDA Fees," Robert Pollock, senior advisor and outside director to the board at Lachman Consultants, wrote in an Oct. 4 blog post on the figures. "But with only a month's warning it is clear that firms tried to clear the decks the best they could."

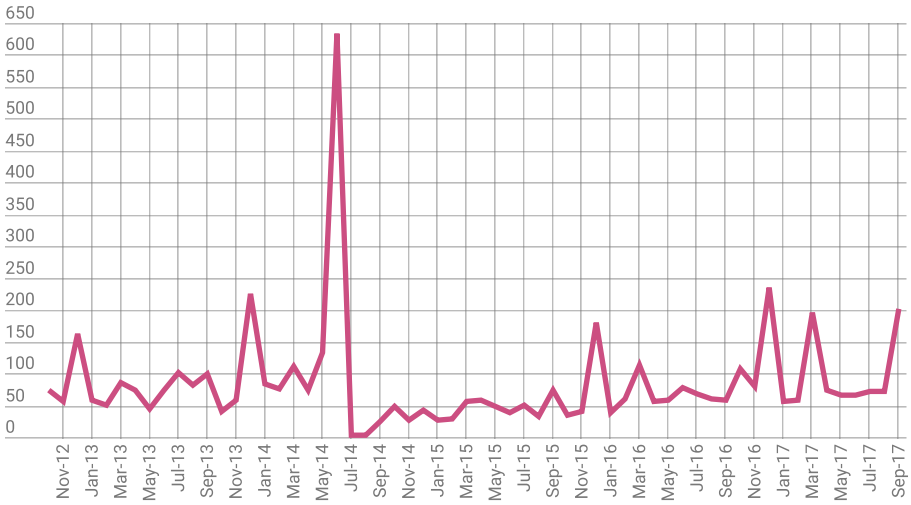
The bolus waited until the final month of the fiscal year to reveal itself. Submission levels had been below average from May through August.

David Gaugh, senior VP of sciences and regulatory affairs for the Association for Accessible Medicines, told the Pink Sheet that it appeared some sponsors anticipated an increase in fees in FY 2018 about a year ago when GDUFA II revenue targets were released and timed their development preparation to result in September filings.

GDUFA II began Oct. 1 with a nearly 53% increase in its overall revenue target. *(Also see "Generic Drug User Fees Will Jump More Than 50% In FY 2018" - Pink Sheet, 16 Oct, 2016.)*

Sponsors made a similar fee-avoidance move in September 2012, before GDUFA I launched. FDA's backlog increased as sponsors submitted applications early because the fee paid for an application that

ANDA Submissions Spike Again...



...And Approvals Rebound To End FY 2017

An ANDA submission bolus arrived in September with user fees set to increase dramatically the following month. At the same time, ANDA approvals also jumped, pushing the average to about 63.6 per month in FY 2017, the highest yearly average seen in GDUFA I.

Source: FDA generic drug program activity report

was pending at program launch was less than the actual application fee. *(Also see "Backlog Backfire: FDA Sees Increase In Pending Generic Applications At Deadline" - Pink Sheet, 15 Oct, 2012.)*

FY 2017 DEFINED BY ANDA RUSHES

The rush in September was one of several that appeared in FY 2017 as sponsors worked to clear their books at the end of the year or take advantage of new user fee goals.

In October 2016, the first month of FY 2017, sponsors sent 108 applications as most were expected to gain 10-month user fee goals. *(Also see "Another ANDA Submission Surge Begins" - Pink Sheet, 21 Nov, 2016.)*

Then in December 2016 as sponsors worked to finish pending work before the end of the calendar year, another 235 ANDAs were submitted. *(Also see "ANDA Stress Test: End-Of-Year Submission Bolus Pressures US FDA Review System" - Pink Sheet, 9 Jan, 2017.)* And in March 2017, in what was thought to be the result of firms in India looking to finish work before the end of that country's calendar year, another bolus of 197 ANDAs was submitted. *(Also see "Generic Drug Puzzle: Why Did ANDA Submissions Spike Again?" - Pink Sheet, 11 Apr, 2017.)*

The four bolus months accounted for more than 57% of all the ANDAs submitted in FY 2017.

FDA averaged nearly 108 submissions per month in FY 2017, which is much higher than every other year in GDUFA I, except FY 2014. That year the agency received more than 122 submission per month, it was almost entirely due to the 635 applications received in June 2014.

The famous application rush was due to sponsors attempting to avoid new stability requirements that were about to be imposed. *(Also see "ANDA Avalanche: How Will FDA Deal With The 600 Received This Month?" - Pink Sheet, 30 Jun, 2014.)*

APPROVAL VOLUME FINISHES YEAR WITH A FLOURISH

OGD ended FY 2017 with a new high for approvals.

The agency posted 70 approvals in September. It was the third month of the previous five where the agency posted at least 70 approvals. OGD logged 763 approvals for all of FY 2017, which was the highest total for GDUFA I by more than 100, part of a steady trend upward as OGD improved its approval volume. *(Also see "ANDA Approvals Break Record, May Set New Normal" - Pink Sheet, 10 Jul, 2017.)*

In GDUFA II, the agency will be looking to increase approvals further with a 10-month standard review goal in place for all applications as well as the possibility of an eight-month priority review for those that qualify. *(Also see "ANDAs Can Get Priority, Eight-Month Reviews Under User Fee Deal" - Pink Sheet, 24 Sep, 2016.)*

Increasing generic competition also is a priority for Commissioner Scott Gottlieb, who wants FDA to help lower drug costs for consumers. *(Also see "Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff" - Pink Sheet, 16 May, 2017.)*

Gottlieb also has prioritized streamlining the complex generic approval process. FDA recently unveiled a new web portal for sponsors to submit and track pre-ANDA meeting requests.

Sponsors can schedule product development or pre-submission meetings with the agency to discuss equivalence approaches early in development or novel items that will appear in the application package, respectively. *(Also see "Complex ANDAs: Early Meetings With FDA Can Generate Bonus Communication" - Pink Sheet, 2 Oct, 2017.)*

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FDA PASSES PDUFA SPENDING REVIEW

The HHS Inspector General found that FDA was spending prescription drug user fee dollars appropriately, according to a report announced Oct. 5. No recommended changes were offered.

FDA did not have adequate supporting documents for $6,403 in travel expenses, but the IG concluded that it appeared to be an oversight rather than a systemic issue. The agency also overpaid a traveler $587 and made a duplicate airfare payment of $1,213, but both were recovered during the review, according to the report.

The IG review included documents related to the $796.1m in PDUFA revenue reported during FY 2015.

PBM Controls Coming To Medical Benefit Drugs? Express Scripts Acquisition Offers Platform

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Express Scripts Holding Co. may be able to apply the cost management and rebate negotiation programs it currently uses in retail pharmacy to high-cost prescription drugs reimbursed under the medical benefit with the planned acquisition of medical benefits management company, eviCore.

The pharmacy benefits manager announced Oct. 10 it has agreed to buy privately-held eviCore for $3.6bn from the company's current investors, General Atlantic, TA Associates and Ridgemont Equity Partners. The transaction is expected to close in the fourth quarter.

The deal has significant implications for specialty drug pricing. "I think the most intriguing opportunity for ESI here is the potential for market share manipulation in the medical specialty drug space," Solid Benefit Guidance Area Senior VP Josh Golden told the Pink Sheet.

"Unlike on the pharmacy benefit side where rebates are heavily scrutinized by plan sponsors, medical specialty rebates fly largely under the radar right now," he added. "If ESI can leverage eviCore's platform to influence utilization patterns and product mix, they have an opportunity to tap into that rebate flow." Solid Benefit Guidance is a division of Arthur J. Gallagher.

EviCore offers benefit management programs to help payers reduce medical costs in radiology, cardiology, musculoskeletal health, medical oncology, radiation therapy, sleep therapy, lab management and post-acute care. It also offers a program in specialty drug management that involves ensuring provider adherence to evidence-based guidelines and enforcing the plan's formulary.

The company has over 100 million individuals on its platform that are enrolled in managed care organizations and risk-bearing provider organizations in the commercial, Medicare and Medicaid markets.

Express Scripts agreed the purchase could help it exert more control over medical drug costs through formulary negotiations and rebates, a long-sought goal. "It helps our ability to do more there, for certain," a spokesperson said. "How exactly that will take shape is to be determined."

Drugs reimbursed under the medical benefit are mostly injectable or intravenous treatments administered in physician offices or clinics under the supervision of a trained health care provider. There are a number of challenges involved in managing the cost of those treatments, include billing practices that combine the cost of a drug with its administration (leading to limited visibility on pricing), differences in cost based on site of care and provider reliance on drug dispensing revenues.

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> "We're looking at gene therapy, for example, as an area where novel reimbursement strategies are necessary," an Express Scripts spokesperson said.

Insurers apply utilization management tools like prior authorization to control use of expensive drugs and there is some rebating tied to formulary negotiation. But not to the extent that it exists for retail pharmacy drugs. The big PBMs currently focus cost control efforts on drugs covered under the pharmacy benefit, which are usually orals or self-administered treatments.

"We believe that our work in specialty [drugs] is well documented – delivering better outcomes at lower costs for drugs that are increasingly taking up a greater share of the payer budget," the Express Scripts spokesman added. But "that is only on the pharmacy side."

The company is now actively working on opportunities on the medical benefit side. "We're looking at gene therapy, for example, as an area where novel reimbursement strategies are necessary," the spokesman pointed out. Express Scripts Chief Medical Officer Steve Miller signaled the company's interest in participating in the development of pricing and payment policies for gene therapies during a recent conference in Washington, D.C. *(Also see "Novartis Set 'Responsible' Price For Kymriah, Express Scripts Says" - Pink Sheet, 13 Sep, 2017.)*

Other medical benefit drugs that might lend themselves to cost controls include cancer immunotherapies in crowded markets, such as in lung or bladder disease, where competition could help drive down prices. PBM tactics could also help promote the use of biosimilars.

A TRANSFORMATION INTO A 'PATIENT BENEFIT MANAGER'

The acquisition is framed mainly as a way for Express Scripts to broaden its set of cost management solutions. It "gives us an entry where we can do more to bring down the cost of healthcare," the spokesperson said. "We have core competencies in pharmacy

management and we're adding the ability to apply those competencies in medical benefit management with a company, eviCore, that does this very well."

In a joint release on the acquisition, the companies emphasized the growth potential of the market served by eviCore.

"Medical benefit management is a large and growing market with more than $300bn spend annually in the areas eviCore manages today," the companies said. "Establishing a cornerstone platform in this market will enable Express Scripts to build a uniquely comprehensive suite of solutions, with significant opportunities for cross-selling to both client bases."

The addition of the medical benefit management operation "will further differentiate Express Scripts and position the company to take advantage of the transition to value-based care and the increasing demand from payers for a more comprehensive set of service offerings and solutions. ... Together with eviCore, Express Scrips will be an even more powerful partner in managing costs for patients and payers, bringing us closer to our goal of becoming the nation's leading patient benefit manager."

The move comes as Express Scripts is facing a number of business headwinds. The first is the prospect of losing its largest customer, **Anthem Inc.**, in 2019 after a dispute over allegations that the PBM overcharged the insurer by billions of dollars. *(Also see "Express Scripts-Anthem Split Could Signal Positive Trend For Biopharma" - Pink Sheet, 25 Apr, 2017.)*

It also comes amid speculation that online behemoth Amazon is considering a move into mail-order pharmacy sales, which could significantly disrupt the prescription drug supply chain. Finally, the PBM business model, with its reliance on drug rebates, have faced ongoing public criticism as part of the broader drug pricing debate, reigniting calls for greater transparency in the drug supply chain.

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CONSUMER PRODUCTS

FDA Objects To Amarin Trade Complaint Against Omega-3 Ingredients

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"In short, in order to resolve any of [Amarin's] claims, the Commission will necessarily have to step into the shoes of the FDA to interpret, apply, and enforce the FDCA. The FDCA precludes such action."
– FDA Chief Counsel Rebecca Wood

FDA's chief counsel says Amarin Corp. PLC's request for the International Trade Commission to effectively shut down a large piece of the US omega-3 dietary supplement market is interfering with the agency's authority to regulate the industry.

Amarin filed a complaint with the FTC Aug. 30 asking it to investigate importation and sale of synthetically produced omega-3 products by 18 companies, with the aim of protecting the market for its Rx drug *Vascepa* (icosapent ethyl), a synthetically produced ethyl ester approved to reduce triglyceride levels in adults with severe hypertriglyceridemia. *(Also see "Amarin Seeks ITC Action Against Products 'Cloaked' As Dietary Supplements" - Pink Sheet, 30 Aug, 2017.)*

Amarin contends that dietary supplements containing purified eicosapentaenoic acid (EPA) or omega-3 formulations containing primarily EPA in ethyl ester or re-esterified form are actually drugs, and asks the trade commission to block import of those ingredients by a number of companies.

In an Oct. 6 letter asking ITC not to take up Amarin's complaint, FDA Chief Counsel Rebecca Wood states that "even if the Complainants have pled a viable claim … FDA believes that the Commission should decline to initiate an investigation under principles of comity to FDA – the federal agency that has the congressionally delegated authority to determine the status of the products at issue." The letter also is signed by Anna Abram, deputy commissioner for policy, planning, legislation and analysis.

ITC, a division of the US Department of Commerce, has extended its consideration

of whether to investigate the firm's complaint through Oct. 20. If the commission initiates an investigation it will assign the case to an administrative law judge, who will set a target date for completion of the investigation.

Wood says that should ITC consider Amarin's complaint and find for the firm, its ruling could conflict not only with finalized FDA policies, but also with rulemakings, guidances and other documents currently in development, including guidances on new dietary ingredient (NDI) notifications and on determining whether an ingredient is an NDI.

She said Amarin "is mistaken" in asserting that its arguments "do not turn on open questions or policy" under the Food, Drug and Cosmetic Act.

OMEGA-3S NARROWLY, ALL SUPPLEMENTS BROADLY

The complaint narrowly targets the US market for omega-3 supplements containing ethyl ester or re-esterified EPA to enhance bioavailability, but more broadly challenges FDA's criteria for allowing the use of certain ingredients in supplement products.

It requests an order halting imports by 18 companies that sell synthetically produced omega-3 oil as dietary supplement ingredients or as finished products or encapsulated synthetically produced omega-3 oil with purified EPA or omega-3 fatty acid mixtures that are predominantly EPA in ethyl ester or re-esterified form. *(Also see "Amarin's Omega-3 Fair Trade Complaint Questions US Dietary Ingredient Standards" - Pink Sheet, 7 Sep, 2017.)*

Amarin argues that before these types of omega-3 fish oils were used as dietary ingredients they were the subject of investigational new drug programs, which would preclude their use as dietary ingredients under the Dietary Supplement Health and Education Act, the 1994 legislation that established FDA's framework for regulating the supplement industry.

Supplement industry stakeholders say the types of omega-3 that Amarin is challenging were present in the food supply long before they were IND candidates in the 1980s and they contend that the firm's request is an attempt to block US consumers' access to products that are entirely compliant with FDA regulations. The Council for Responsible Nutrition submitted a letter to ITC saying that FDA finds the products entirely compliant and that Amarin's argument for its false advertising claim has repeatedly been dismissed in courts. *(Also see "Amarin Makes Flawed Argument In Bid To Drain Omega-3 Market – CRN" - Rose Sheet, 15 Sep, 2017.)*

> "FDA cannot administer and enforce the FDCA effectively if core FDA issues ... are decided in actions brought by private parties."
> – FDA's Wood

A spokesman said the firm would not comment and an attorney representing Amarin in the ITC complaint declined to comment on FDA's argument.

'ONLY FDA' ENFORCES FDCA

Wood's letter explains why "Congress has authorized only FDA to initiate FDCA [Food Drug & Cosmetic Act] enforcement actions."

"FDA is the expert agency responsible for determining whether products comply with the" FDCA, and is authorized by Congress with "a number of enforcement tools to address the distribution of products in violation of FDCA," she said.

Amarin's claims of violations of US trade and advertising laws as well as FDA regulations "all depend on the allegation that the products at issue" are falsely labeled as dietary supplements because the omega-3 ingredients should be regulated as drugs, Wood said.

"In short, in order to resolve any of [Amarin's] claims, the Commission will necessarily have to step into the shoes of the FDA to interpret, apply, and enforce the FDCA. The FDCA precludes such action," she added.

The FDCA also prohibits enforcement of the agency's regulations by private parties. "FDA cannot administer and enforce the FDCA effectively if core FDA issues – such as whether a product is a 'new drug' or a 'dietary supplement' under the FDCA – are decided in actions brought by private parties, the chief counsel said.

FDA is also worried that Amarin's complaint to ITC could prompt other firms to attempt private party enforcement across FDA's regulatory scope.

Amarin filed suit against FDA in 2015, challenging the agency's regulations on off-label drug promotion and seeking a determination that it could communicate to health care providers information from studies on Vascepa's use by adults on statin therapy for high triglyceride levels. It argued that FDA permits supplement manufacturers to make claims that omega-3 fatty acid products "may" reduce the risk of coronary heart disease and EPA "lowers triglycerides," but forbids the firm from telling doctors that in studies Vascepa lowered triglycerides for patients with persistently high levels in studies. *(Also see "Off-Label Unleashed? Amarin Win Suggests Firms Still Need Strong Data To Skirt FDA" - Pink Sheet, 7 Aug, 2015.)*

A federal judge ruled Amarin may engage in truthful and non-misleading speech about the unapproved use of Vascepa in patients with persistently high triglycerides and that such speech may not form the basis of a misbranding lawsuit. The firm and FDA settled the litigation in an agreement that included an optional preclearance process for the company's future communications about off-label use of Vascepa, which has yet to generate profits for the Dublin-based firm..

Wood's Oct. 6 letter provides a detailed review of FDA's authorities and its process for regulating supplements. She concludes with a reference to the agency's citizen petition process, though not specifically suggesting Amarin submit a petition. "Finally, we note that FDA has, in the past, addressed questions regarding the regulatory status of certain products through the agency's citizen petition process," she said.

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EudraVigilance Update Needs 10-Day IT Shutdown At EMA; Interim ADR Reporting Plans In Place

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The European Medicines Agency has drawn up alternative arrangements for drug companies to report suspected adverse drug reactions during the two weeks some of its systems will be down while it prepares for the launch of the revamped EU pharmacovigilance database, EudraVigilance, in late November.

The new database is due to come online at 9am on Nov. 22. The revamp involves switching to a centralized reporting system and companies are nervous about the change. The shutdown will run from Nov. 8 to Nov. 21, involving ten working days. The interim arrangements will apply to authorized medicines and to medicines that are being studied in clinical trials in the European Economic Area.

The EMA is warning that the full or partial shutdown of some of its IT systems may also impact companies planning to submit periodic safety reports, marketing authorization applications (MAAs) or clinical trial applications during this period. Companies are being advised to pay attention to the affected systems, and to prepare in advance to avoid any disruptions to their business plans and ensure compliance with regulatory requirements. Companies will need to be vigilant as the arrangements are not the same across all member states.

The revamped EudraVigilance database will make it easier for drug companies to report individual case safety reports (ICSRs). It will also introduce new obligations for companies with respect to signal detection. *(Also see "Are You Ready? EU Launches Test Environment For New EudraVigilance System" - Pink Sheet, 27 Jun, 2017.)*

Before the new database can become functional, the EMA must transfer over the 11 million ICSRs that are in the current system to the revamped version of the database. These ICSRs, which are currently formatted as per the International Council for Harmonisation's E2B(R2) standard, must be transferred to the new E2B(R3) format before they can be entered into the new system. According to the EMA's François Domergue, a "downtime" of 10 working days – from Nov. 8 to 21 – has been decided to enable the switch, during which some functionalities of the system will be entirely or partially unavailable.

Domergue, the EudraVigilance business project manager at the EMA, was speaking at the 11th Drug Information Association (DIA) forum for EU qualified persons for pharmacovigilance (QPPV) that took place in London on Oct. 4 – 5. He said the migration of data was a complex process and told delegates: "We looked at a number of options, all of which required some downtime... We balanced the benefits and risks, and decided that this [i.e., requiring a downtime of 10 business days] was the safest option to undertake this complex process, and to ensure that we are able to go live with the new database on Nov. 22 and that there is no roll back or delay at the last minute."

During the downtime period, the EVWEB – the application for electronic reporting of ICSRs for authorized medicinal products, and suspected unexpected serious adverse reactions (SUSARs) for products undergoing clinical trials – will not be available to national competent authorities (NCAs), marketing authorization holders (MAHs) and trial sponsors.

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> "We looked at a number of options, all of which required some downtime."
> – François Domergue, EMA

NO SINGLE POLICY AMONG MEMBER STATES

For reporting of ICSRs during this period, Domergue explained that NCAs and MAHs will have to follow one of the three options, depending on which member state is involved in the reporting process. For example, only the UK and Germany are requiring that MAHs should continue with electronic submission of ICSRs to them during the downtime period, where this is technically feasible. The reporting will have to done in accordance with the interim reporting provisions set out in the guideline on Good Pharmacovigilance Practices (GVP) Module VI. Separate provisions will apply where electronic reporting is not possible during the cutover period.

Hungary, the Czech Republic, Denmark, Greece, Iceland, Romania and Italy will require MAHs to follow alternative arrangements (eg, submissions through email, fax, post etc or following national reporting arrangements) for reporting of adverse reactions during the downtime period. All other NCAs have agreed that no ICSRs should be submitted during this period and that all pending reports can be submitted electronically in accordance with the simplified procedure after the new database becomes operational on Nov. 22. This means that no alternative arrangements for ADR reporting by a MAH to a NCA will apply for these remaining member states.

The alternative arrangements for reporting of ICSRs, as well as

SUSARs, during the downtime period are explained in greater detail in the EMA's "EudraVigilance Go-Live Plan" published on Oct. 4. Margret Walters of Merck, Sharp & Dohme said that the interim plan was "very helpful" but warned that "there is a lot to it" so companies should review it carefully.

Domergue also gave details of other EMA IT systems that will be fully or partially affected during the downtime period. Specifically:

- The extended EudraVigilance medicinal product dictionary (XEVMPD), also known as the Article 57 database, will not be available for electronic submission of data on medicines, including for new entries and updates to existing entries.
- The registration of new organizations or users and updates to existing users in the EudraVigilance Registration System will not be possible.
- The repository for periodic safety update reports (PSURs) will remain, but will be affected as "product selection" for PSUR submissions is linked to XEVMPD. It will not be possible to update/amend product data in the XEVMPD for creating XML delivery files during this period. For affected products, the EMA recommends that MAHs should create the xml delivery file and submit their PSURs before Nov. 8. Where this is not possible, the MAH will have to request "a late submission ID" from the EMA to submit initial PSURs after the due date.
- The EMA's electronic-Application Forms (eAF) service will remain available, but will be affected as "substance selection" for an initial marketing authorization application is linked to the XEVMPD. As a result, it will not be possible to update substance data in the XEVMPD for the creation of the eAF dataset during this period. Companies with a MAA date coinciding with the scheduled downtime are being asked to carefully review the situation and update the relevant data beforehand.

> Registration of new users and updates to existing users in the EudraVigilance Registration System will not be possible during the IT downtime.

- The EU Clinical Trials database (EudraCT) and the EudraCT data warehouse will remain available, but their functioning will also be affected due to the unavailability of the XEVMPD. For example, for protocol data and registration of substance data in the XEVMPD as part of preparing for a clinical trial application, the EMA recommends that entries should be completed befor Nov. 8 or that data submission should take place on or after Nov. 22.

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FDA's NDA And BLA Approvals: Zilretta, Lyrica CR

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				
Flexion	*Zilretta* (triamcinolone acetonide)	Extended-release synthetic corticosteroid for use as an intra-articular injection for the management of osteoarthritis pain of the knee.	S, 5	10/6/2017
Pfizer	*LyricaCR* (pregabalin)	Extended-release formulation to manage neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.	S	10/11/2017

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

Spark's Gene Therapy Luxturna Sails Through US FDA Panel

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A US FDA advisory committee's strong backing of **Spark Therapeutics Inc.**'s *Luxturna* (voretigene neparvovec) for inherited retinal dystrophy at an Oct. 12 meeting came with an endorsement of the sponsor's novel endpoint for assessing the gene therapy's impact on functional vision.

The Cellular, Tissue and Gene Therapies Advisory Committee unanimously concluded that voretigene (AAV2-hRPE65v2) had a favorable risk/benefit profile in patients with vision loss due to a mutation in the RPE65 gene. *(See box)*

The committee members generally found that the improvement seen in the multi-luminance mobility testing (MLMT) endpoint used in the Phase III trial was clinically meaningful. In addition, the MLMT results were generally supported by improvements in visual acuity, visual field and patient-reported quality of life.

Also persuasive were testimonials during the open public hearing from, and on behalf of, approximately a half dozen patients with the rare genetic mutation who spoke about dramatic improvements in their vision and activities of daily living following a subretinal injection with voretigene in each eye.

For many rare disease patients, "their principal hope is that they would arrest disease progression under any circumstances," said Barry Byrne, the panel's acting chairman and professor of pediatric and molecular genetics and microbiology at the University of Florida College of Medicine. "I think this is one unique finding in this study that … that there's actually a reversal of the deficit."

The committee's recommendation leaves voretigene well-positioned to become the first gene therapy approved for treatment of vision loss. The user fee date for Spark's biologics license application (BLA) is Jan. 12.

Looking beyond the voretigene BLA, the panel's endorsement can be viewed as a validation of Spark's approach to developing a novel endpoint with potential applications for other therapeutics to treat vision loss.

> "For people with little or no vision, alternative functional endpoints beyond visual acuity are essential." – Foundation Fighting Blindness' Rose

ENDPOINT UNCERTAINTY

Voretigene is a recombinant adeno-associated virus serotype 2 vector that delivers a functional RPE65 gene with a single subretinal injection.

The primary efficacy outcome in the 21-patient Phase III study was the MLMT, a novel endpoint designed by Spark pursuant to discussions with FDA. The test is intended to measure functional vision by integrating input from visual acuity, visual field and light sensitivity.

The MLMT requires pediatric and adult patents to independently and accurately navigate a course marked by arrows and obstacles within a time limit and under seven different lighting levels, ranging from 1 to 400 lux. Each of the lighting levels is assigned a score from zero to six, and the MLMT score change was determined using the difference in scores between the lowest light levels passed at baseline and year one.

Although FDA agreed that the MLMT could serve as a primary endpoint in the Phase III study, the agency sought the advisory committee's input on the clinical meaningfulness of the median MLMT score change of two light levels in the voretigene-treated group compared to the control arm. *(Also see "Spark's Vision Loss Gene Therapy Raises US FDA Questions About Novel Endpoint" - Pink Sheet, 10 Oct, 2017.)*

"We are uncertain whether the product's activity, as demonstrated by an effect on this novel endpoint, represents a true improvement in the lives of patients," said Wilson Bryan, director of FDA's Office of Tissues and Advanced Therapies.

VIDEOS AND TESTIMONIALS

Spark's presentation to the advisory committee included not only the Phase III data demonstrating statistically significant changes in the MLMT endpoint, but also impactful before-and-after videos showing how subjects' ability to navigate the maze improved with voretigene treatment.

The trial results on the secondary endpoints of visual field and visual acuity testing were favorable, although the latter did not reach statistical significance. Spark also showed results from a visual function questionnaire in which patients reported improvements in activities of daily living.

During the open public hearing, a rep-

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resentative from the Foundation Fighting Blindness, which has financially supported voretigene's development, said the increased functional vision resulting from the gene therapy is clearly shown by the MLMT maze results.

"Not only do we believe this therapy brings a life-changing benefit to our constituents affected by RPE65 mutations, but it also brings a step forward in recognizing that for people with little or no vision, alternative functional endpoints beyond visual acuity are essential," said Stephen Rose, the foundation's chief research officer.

The foundation "believes the validated MLMT maze presented here is a worthy and relevant endpoint that can measure functional vision gained for our constituents with inherited rare retinal degenerations when there is little remaining vision," Rose said. "Therefore, we strongly support the MLMT maze as a new and innovative relevant endpoint for our constituents and for this therapy."

The panel also heard testimony from patients who spoked about the positive, life-altering effects they experienced following voretigene treatment in Spark's clinical trials.

"I remember opening my eye to a bright, colorful world," clinical trial participant Misty Lovelace said. "Before surgery my vision was dark. It was like sunglasses over your eyes while looking through this little tunnel."

"Within days of the first surgery, I could see vibrant colors again. I was no longer living in a black and white film," said Katelyn Corey.

"I was independent and mobile, which I had not been for some time," Corey said. "I may not have gained all of my vision, but I gained all of my independence. I just want you to know that this was significant to me, significant in the way that I live and plan my life."

> "I believe that very detailed studies would be required before we could be certain re-administration is safe."
> – Spark's High

CONVINCED ABOUT CLINICAL BENEFIT

The clinical data and patient testimony left the committee members convinced that the MLMT results were clinically meaningful.

"From the standpoint of a practicing ophthalmologist who sees patients with inherited retinal degenerations every week, I think that this is a meaningful change," said Brian Brooks, clinical director of the pediatric, developmental and genetic ophthalmology unit at the National Eye Institute. "I think that increasingly for patients with very low vision that looking … as quantitatively as we can at what are activities of daily living is a very important thing. I think the sponsor has done a good job of convincing us."

Constance West, a pediatric ophthalmologist in Belmont, Mass., echoed Brooks' comments about the MLMT. "It's not a perfect tool yet, but it's way better than what we have with visual fields and high contrast visual acuity."

Terence Flotte, chief research officer at the University of Massachusetts Medical School, said that while the MLMT change appeared to be clinically meaningful, he also was persuaded by the PRO data and the patient accounts.

"While I can recognize the wisdom in not trying to power a study [based on] the quality-of-life questionnaire … I think that adds confidence to the fact that one might be basing the efficacy judgement off of a novel assay," Flotte said.

AGE LIMIT AND REPEAT USE

The panelists were split on whether there should be a minimum age for treatment with voretigene. Spark is proposing that the therapy be limited for use to patients ages three years and older; the youngest child in the pivotal trials was four years old.

The company also made clear it is not seeking approval for repeat administration despite FDA's question to the committee about the potential benefits and risk of repeated use.

"Based on the durability of Phase III data, we are not recommending repeat administration," said Katherine High, Spark's president and head of R&D. "We have not studied this in clinical development. There are theoretical risks involved with repeat administration."

High pointed to data suggesting that there is some systemic exposure to the vector, which could have immunogenicity implications with repeat dosing.

"To me what this means is that the person at second administration is not the same person as at the first administration," High said. "That to me is one reason that I believe that very detailed studies would be required before we could be certain re-administration is safe."

The company is proposing to limit distribution of voretigene to between five and eight Centers of Excellence in the US with expertise in treating inherited retinal dystrophies.

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ADVISORY COMMITTEE VOTE

Does voretigene neparvovec have an overall favorable benefit/risk profile for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy? **Y – 16, N – 0**

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Spark Therapeutics' *Luxturna* (voretigene neparvovec) for treatment of vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy	Cellular, Tissue, and Gene Therapies	Oct. 12
Aerie Pharmaceuticals' *Rhopressa(*netarsudil ophthalmic solution 0.02%) for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Dermatologic and Ophthalmic Drugs	Oct. 13
Novo Nordisk's semaglutide injection as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Endocrinologic and Metabolic Drugs	Oct. 18
Indivior Pharmaceuticals' buprenorphine subcutaneous injection for treatment of opioid dependence	Psychopharmacologic Drugs/Drug Safety and Risk Management	Oct. 31
Braeburn Pharmaceuticals' buprenorphine subcutaneous injection for treatment of opioid dependence	Psychopharmacologic Drugs/Drug Safety and Risk Management	Nov. 1
Clinical development plan for Pfizer's Staphylococcus aureus vaccine intended for pre-surgical prophylaxis in elective orthopedic surgical populations	Vaccines and Related Biological Products	Nov. 7
Bayer HealthCare Pharmaceuticals' ciprofloxacin inhalation powder for reduction of exacerbations in non-cystic fibrosis bronchiectasis adult patients (≥18 years of age) with respiratory bacterial pathogens	Antimicrobial Drugs	Nov. 16

Pink Sheet

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