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Novartis CAR-T Therapy's Swift Approval Aided By REMS And New US FDA Review Model

BRENDA SANDBURG brenda.sandburg@informa.com

FDA's swift approval of **Novartis AG**'s chimeric antigen receptor T-cell therapy *Kymriah* (tisagenlecleucel) was aided by the company's Risk Evaluation and Mitigation Strategy (REMS), which requires hospitals dispensing the treatment to be certified.

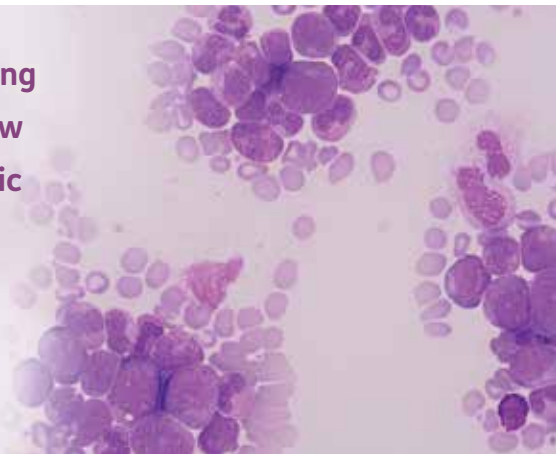
FDA approved Kymriah, the first gene therapy to clear the agency, on Aug. 30 for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. During a media conference call, CEO of Novartis Oncology Bruno Strigini noted that 23 treatment centers would be certified within one month, and the number would expand to 32 by the end of the year.

The therapy is priced at $475,000 for a one-time treatment. Approximately 3,000 patients ages 20 years and younger are diagnosed with ALL each year. Novartis said that since Kymriah's indication is for relapsed or refractory ALL, about 600 patients would be eligible for treatment.

APPROVAL FOLLOWS ADCOMM ENDORSEMENT

Novartis' extensive preparations around a risk mitigation strategy and a postmarketing study helped smooth the path to early approval.

Novartis' postmarketing safety study will follow at least 1,000 pediatric and young adult patients for 15 years after receiving the CAR-T therapy.



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FDA's Oncologic Drugs Advisory Committee voted unanimously to recommend approval of the treatment at a July 12 meeting. Committee members said they were reassured by the company's REMS and its stringent criteria for selecting clinical sites to administer the product. Kymriah therapy will initially be limited to 30-35 centers that meet Foundation for the Accreditation of Cellular Therapy standards and have experience with T-cell therapies and leukemia. *(Also see "Novartis CAR-T Site Selection, Risk Management Are Model For Other Sponsors" - Pink Sheet, 12 Jul, 2017.)*

Novartis will train centers on processes for cell collection, cryopreservation, transport, chain of identity and logistics. In addition, an authorized representative will be designated at each site.

In addition to the REMS, the company has a postmarketing requirement to conduct a prospective, observational study to assess the long-term safety of Kymriah and the risk of all secondary malignancies occurring after treatment with the product.

FDA's approval letter notes that the study will include at least 1,000 pediatric and young adult patients with relapsed/refractory B-cell ALL who will be followed for 15 years after the product is administered.

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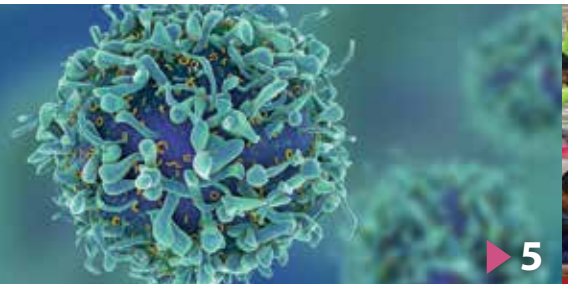
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FDA Eyeing Other PD-1/L1 Drugs With Clinical Hold On Keytruda Myeloma Trials

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Merck previously disclosed the clinical hold on the three trials at the beginning of July; FDA says its announcement is meant to inform patients and healthcare providers about the danger of the safety signal.

CMS Proposal On Part D May Address Drug Costs, But Will It Target Prices?

https://pink.pharmamedtechbi.com/PS121443

Upcoming proposed rule on Medicare Part D and Medicare Advantage prompts speculation about whether CMS is planning new measures to control spending on prescription drugs.

Australia Consults On Advertising Reforms, Allowing Direct Promotion Of Pharmacist-Only Drugs

https://pink.pharmamedtechbi.com/PS121437

Australia's healthcare products regulator wants to develop a new Therapeutic Goods Advertising Code to support a more self-regulatory approach to the way drugs and medical devices are promoted to the public. It has also recommended allowing direct advertising of pharmacist-only medicines, subject to certain controls.

Have FDA Studies Changed Rx Drug Advertising?

https://pink.pharmamedtechbi.com/PS121421

FDA answers questions on the impact its research projects have had since the first Rx drug TV commercial aired in 1983.

US FDA Changes Data Source For GDUFA II Facility Fee Setting

https://pink.pharmamedtechbi.com/PS121420

Agency primarily uses application data instead of facility self-identification lists to determine FY 2018 generic drug user fees.

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CONTINUED FROM COVER

The study is to be completed by Dec. 31, 2037 and a final report submitted by Dec. 31, 2038.

The agency also awarded the company a rare pediatric disease priority review voucher, entitling it to designate another drug application for priority review or to sell the voucher to another company.

"This is an historic moment in the fight against cancer. It marks the first CAR-T cell therapy to be approved anywhere in the world," Novartis CEO Joseph Jimenez said on the call. He noted that relapsed ALL is the leading cause of cancer death in children and that those with relapsed or refractory disease only live a median of three to nine months when treated with currently available therapies.

NEW CROSS-AGENCY APPROACH PUSHED FORWARD APPROVAL

Kymriah is a genetically modified autologous immunocellular therapy in which a patient's own T cells, a type of white blood cell known as a lymphocyte, are collected, cryopreserved and sent to Novartis' manufacturing facility in Morris Plains, NJ. There, the cells are genetically modified to include a new gene that contains a chimeric antigen receptor protein that directs the T-cells to target and kill leukemia cells that have a CD19 antigen on the surface. Once the cells are modified, they are infused back into the patient.

Kymriah was approved based on the results of a pivotal, open-label, single-arm Phase II trial in which 83% of 63 patients who received a single intravenous infusion achieved complete remission or complete remission with incomplete blood count recovery within three months of infusion.

FDA received the BLA on Feb. 2 and approved it almost five weeks ahead of the Oct. 3 user fee goal date.

During an FDA media briefing on the approval, Commissioner Scott Gottlieb said the approval involved a cross-agency approach in which the agency's top oncologists and gene therapy experts worked together to help ensure Kymriah would be available as quickly as possible.

He thanked FDA staff and the leaders at the Center for Biologics Evaluation and Research and the agency's newly established Oncology Center of Excellence, which cuts across medical products centers, for their collective efforts to make the approval possible. "They worked to pioneer and implement this more collaborative scientific model for drug review at FDA," he said.

> CBER and the Oncology Center for Excellence "worked to pioneer and implement" a more collaborative scientific model for drug review at FDA, Gottlieb said.

"This program alignment is an organizational approach that we intend to pursue more widely at FDA across other therapeutic areas as a way to improve our efficiency and deepen our scientific collaboration," Gottlieb said.

ACTEMRA GAINS A NEW INDICATION, TOO

FDA also granted expanded approval to **Genentech Inc.**'s interleukin-6 receptor antagonist *Actemra* (tocilizumab) intravenous injection for treatment of CAR-T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients two years of age and older.

Genentech noted in a release that this is the first FDA-approved treatment to manage CRS associated with CAR-T cell therapy.

Kymriah's label includes a boxed warning about the occurrence of CRS, including fatal or life-threatening reactions, in patients receiving Kymriah. It says the therapy should not be administered to patients with active infection or inflammatory disorders.

The boxed warning also states that "neurological toxicities, which may be severe or life-threatening, can occur following treatment with Kymriah, including concurrently with CRS."

FDA's advisory panel discussed the risks of CRS and neurotoxicity and considered them to be generally manageable. The committee concluded that the efficacy of Kymriah and the lack of treatment options outweighed any concerns. One panel member noted that standard chemotherapy and hematopoietic stem cell transplant have limited efficacy, and patients who relapse post-transplant have a two-year overall survival rate of 15%. *(Also see "Novartis' CAR-T Poised For The Market After Unanimous FDA Adcomm Review" - Scrip, 12 Jul, 2017.)*

PRICING COLLABORATION WITH CMS

While Kymriah has established a bar for the approval of gene therapies, it also has broken new ground with a unique pricing strategy.

Under an innovative outcomes-based pricing approach with the Centers for Medicare and Medicaid Services, for Kymriah's initial indication there will be no charge for the therapy if the patient does not respond by the end of the first month of treatment.

"This is the first of a kind, pay-for-performance arrangement with CMS," Jimenez said on the media call.

Novartis said this potentially supports lower prices for future indications if the value delivered from the therapy is lower.

The company noted that it will be filing for diffuse large B-cell lymphoma (DLBCL), which accounts for approximately 30% of all non-Hodgkin lymphoma cases, in the US in the fourth quarter. Novartis said that 10% to 15% of DLBCL patients fail to respond to initial therapy or relapse within three months of treatment, and an additional 20% to 25% relapse after initial response to therapy.

A company official noted on the call that since the remission rates are lower in DLBCL than in pediatric ALL, if there were indication-based pricing it might lead to lower prices. "It all depends on the results and outcomes the particular therapy delivers," he said.

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Novartis Begins CAR-T Payment Experiments With Outcomes-Based Contract With CMS

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Novartis AG's newly-approved CAR-T treatment for childhood leukemia, *Kymriah* (tisagenlecleucel), will be reimbursed based on outcomes under a groundbreaking arrangement between the manufacturer and the Centers for Medicare and Medicaid Services.

Kymriah was cleared by FDA Aug. 30 for pediatric and young adult patients with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse. It is a one-time, single administration treatment and has a list price of $475,000.

Novartis did not specify whether its arrangement with CMS is specific to Medicaid or Medicare (or both). However, Kymriah's initial indication is for children and young adults, which would generally be covered by Medicaid. Future indications in adults might be covered by Medicare.

Novartis is "collaborating with CMS to make an outcomes-based approach available to allow for payment only when pediatric and young adult ALL patients respond to Kymriah by the end of the first month," the company said in an Aug. 30 release.

Novartis said it also expects to work with private insurers on outcomes-based contracts for Kymriah and hopes to develop similar arrangements for other treatments. The arrangement will likely set a precedent for other CAR-T treatments.

"Novartis has been at the forefront of outcomes-based pricing and is very pleased to work with CMS on this first-of-its-kind collaboration with a technology that has the potential to transform cancer care," Novartis CEO Joseph Jimenez said. "We look forward to continuing to work with CMS to potentially expand this approach to other products and disease states."

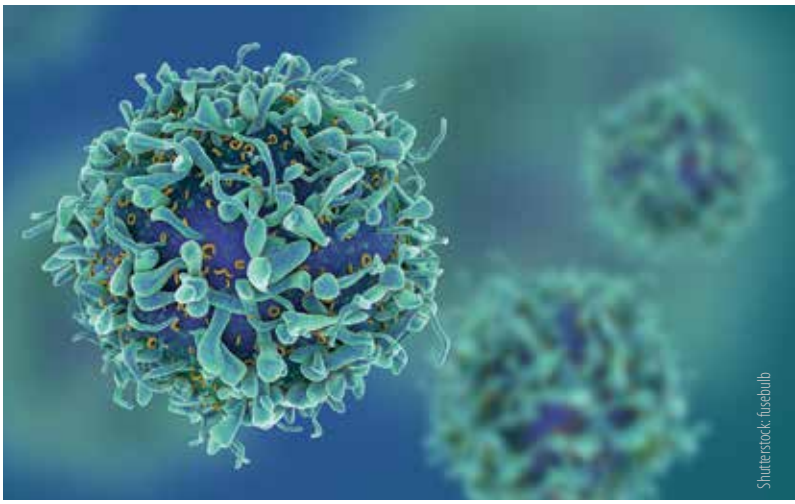
INDICATION-BASED PRICING UNDER DISCUSSION

The arrangement is part of a broader discussion between Novartis and CMS on performance-based reimbursement models for Kymriah.

For example, the company is working with the agency on developing indication-based pricing for the treatment as additional uses are approved in the future. Depending on the data, new indications could require a different cost effectiveness calculus, and potentially, lower payments, the company noted. Novartis is planning to file an application for Kymriah in the treatment of adult patients with diffuse large B-cell lymphoma later this year.

Although the patient group covered by the initial performance-based arrangement for Kymriah is likely to be relatively small – the company estimates 600 patients per year will be eligible for treatment – the fact that it involves CMS may go a long way toward advancing outcomes-based contracts.

One benefit could be that the details around outcomes are made public under the government contract, which currently is not the case with existing performance-based contracts in the private insurance market.



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> Starting out with an outcomes-based agreement with CMS may go a long way in advancing other contracts.

"Because this is with CMS, we will (or at least I fully anticipate) be able to see all the payment rules and endpoints and ultimately be able to evaluate them," Memorial Sloan Kettering's Peter Bach told the *Pink Sheet*. "That will make this distinct from essentially all the [outcomes-based contracts] out there, which are proprietary." Bach is director of the Memorial Sloan Kettering Center for Health Policy and Outcomes and a frequent commentator on drug pricing policy.

The multi-stakeholder Council for Affordable Health Coverage also hailed the Novartis/CMS agreement as an important advance. The council represents payers, patients, physicians and biopharma firms.

"While we await more specific details of the agreement reached between Novartis and CMS, we believe this arrangement will be a win for patients, as it recognizes the need to reward outcomes and ensure the cost of treatment is a reflection of its clinical success," President Joel White said in a release. "CAHC applauds CMS and Novartis on this announcement with the hope that it will be a catalyst for a broader, system-wide shift in health care towards value-based reimbursement."

David Mitchell, Founder and President of Patients For Affordable Drugs, was less complimentary about the Kymriah pricing and reimbursement strategy, however.

"While Novartis's decision to set a price at $475,000 per treatment may be seen by some as restraint, we believe it is excessive," Mitchell said in an Aug. 30 statement. "Novartis should not get

credit for bringing a $475,000 drug to market and claiming they could have charged people a lot more."

The company said in a same-day conference call with reporters that its own assessment revealed Kymriah would be cost-effective in pediatric ALL at $600,000 to $750,000 for the one-time treatment, but pricing was set lower to support the health care system and ensure patient access.

CMS WILL ISSUE GUIDANCE TO BIOPHARMA ON NOVEL CONTRACTS

CMS issued a statement on the Kymriah approval to announce it is committed to working with manufacturers and other stakeholders on ways to better manage the cost of cutting-edge treatments.

"Innovations like this reinforce our belief that current healthcare payment systems need to be modernized in order to ensure access to new high-cost therapies, including therapies that have the potential to cure the sickest patients," CMS Administrator Seema Verma said. "Improving payment arrangements is a critical step towards fulfilling President Trump's promise to lower the cost of drugs."

CMS also plans to issue guidance to explain how other pharmaceutical manufacturers "can engage in innovative payment arrangements," Verma added. The agency "will continue to work with states on other options as well [to] help them manage the cost of new therapies and cures."

She pointed out that the CMS can work through the Center for Medicare and Medicaid Innovation to "aim to identify and alleviate regulatory barriers in Medicare and Medicaid as may be necessary to test payment and service delivery models that involve value-based payment arrangements."

Medicaid programs currently are required to cover drugs as long as manufacturers agree to provide the statutorily defined rebates. As a result, Medicaid would not have much price negotiating leverage for a drug like Kymriah.

KYMRIAH PRICE AIMS FOR ACCESS, NOVARTIS SAYS

Novartis maintained that in setting the price for Kymriah, the company aimed to come in below the level identified in cost effectiveness analyses of the treatment, including an evaluation by the UK's National Institute for Health and Care Excellence (NICE). The company also sought to set the price below the current standard of care for an allogeneic stem cell transplant, which it said is $540,000 to $800,000.

In the US, the Institute for Clinical and Economic Review is planning a cost effectiveness analysis of its own covering Kymriah and **Kite Pharma Inc.**'s pending CAR-T treatment, axicabtagene ciloleucel. *(Also see "ICER's Ambitious 2018 Review Agenda Takes On Groundbreaking Treatments" - Pink Sheet, 10 Aug, 2017.)* A draft evidence report is scheduled to be released in mid-December, followed by a final report in February 2018.

Because ICER is in the process of its analysis, President Steve Pearson declined to comment on Kymriah's price. However, he offered some general comments on the pricing environment for such therapies.

"It is a very exciting day for innovation, for science, for patients," he said in an interview. "But we shouldn't forget what else happened today. What else happened today is a company, albeit one that obviously took business risks and sank a lot of money into this … got to name their price."

He added, "Unlike a car company where people can go next store and shop for a different model, patients are going to want this drug and taxpayers and public and private insurers are going to pay this price. So it just kind of highlights the unique landscape for drug pricing in this country and the questions around how we talk about an accountable system for making sure the price aligns with benefit and does support this kind of innovation going forward."

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Humira Biosimilar: Boehringer Faces Same Launch Hurdles As Amgen

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While **Boehringer Ingelheim Pharmaceuticals Inc.** is the second company to win US approval of a biosimilar to **AbbVie Inc.**'s *Humira* (adalimumab), its launch date is uncertain given ongoing patent infringement litigation.

As a sign of the marketing delay, as of Aug. 2, the date AbbVie filed an infringement suit, BI had not yet provided AbbVie 180-day notice of its intent to commercialize its biosimilar, *Cyltezo* (adalimumab-adbm). FDA approved the anti-tumor necrosis factor antibody, previously known as BI 695501, on Aug. 25. *(Also see "US Approvals Roundup: Cyltezo Biosimilar, Victoza CV Benefit, Gocovri In PD, Kedrab Rabies Biologic, Gout Combo Duzallo" - Pink Sheet, 27 Aug, 2017.)*

AbbVie's complaint, filed in the US District Court for the District of Delaware, says AbbVie has identified 74 patents as being infringed but that BI has opted to cap the number in the litigation to eight, as permitted under the Biologics Price Competition and Innovation Act.

"While AbbVie is only permitted to assert eight patents now, if and when Boehringer provides its 180-day Notice of Commercial Marketing, and as circumstances otherwise warrant, AbbVie will have the opportunity to assert the remainder of the patents," the complaint states. "Therefore, there will be a second wave of litigation to adjudicate AbbVie's substantial patent

rights relating to Humira."

The patent battle mirrors that between AbbVie and **Amgen Inc.**, which received approval of its Humira biosimilar *Amjevita* (adalimumab-atto) in September 2016. Just before the approval, AbbVie filed suit claiming infringement of 61 patents and Amgen limited the number to be litigated to 10. *(Also see "AbbVie v. Amgen Round One: Humira Biosimilar Infringes 10 Patents, Suit Claims" - Pink Sheet, 5 Aug, 2016.)*

Amgen has said it doesn't plan to launch Amjevita until at least 2018 given the complexity and pace of the litigation.

[Editor's note: BI said it could not speculate on the launch timing of Cyltezo or comment on ongoing litigation with AbbVie. In an Aug. 29 press release announcing approval of Cyltezo in a pre-filled syringe, BI noted that it will also seek approval for an auto-injector version of the biosimilar as another delivery option for patients.]

Humira, a therapeutic antibody to human TNF-α, a protein made as part of the body's immune response, is the world's top selling drug. It generated more than $16bn of revenue in 2016.

WHAT MANUFACTURING PROCESS INFO IS ENOUGH?

In June, the Supreme Court ruled in **Sandoz Inc.** v. Amgen that biosimilar sponsors may provide 180-day notice of marketing prior to FDA approval.

BI's delay in providing commercialization notice may reflect that it will be awhile before it is able to go to market, for manufacturing or other reasons, said Chad Landmon, a partner at Axinn, Veltrop & Harkrider.

The move also delays litigation over additional patents and there could be a cost or strategic reason for BI to want to hold off on facing AbbVie's entire patent portfolio, Landmon said. "Often a small handful of patents are representative of others or are the most critical, and it could be Boehringer wants to take care of those first."

AbbVie notes in its complaint that BI has engaged in the information exchange process, known as the patent dance, and that the two have negotiated the patents to be subject to initial litigation. But AbbVie says that although BI provided access to its aBLA it did not provide any other manufacturing process information beyond what is in the application. This could become an issue in litigation, as it was in Amgen's suit against **Hospira Inc.** (now **Pfizer Inc.**).

Boehringer Ingelheim

> Like Amjevita, Cyltezo is approved for seven of the 10 indications on Humira's label: rheumatoid arthritis; juvenile idiopathic arthritis; psoriatic arthritis; ankylosing spondylitis; adult Crohn's disease; ulcerative colitis; and plaque psoriasis.

Amgen claimed Hospira refused to produce complete information regarding the composition of the cell-culture medium it uses to manufacture a biosimilar to Amgen's *Epogen* (epoetin alfa). Amgen argued that without this information it could not assess whether its manufacturing process patents were infringed. The Delaware district court denied Amgen's motion to compel discovery from Hospira on the composition of its cell-culture medium concluding that the information has no relevance to the patents asserted in the litigation. *(Also see "Biosimilar Barricade Breached: Amgen Manufacturing Patents Ruled Not Infringed" - Pink Sheet, 7 Sep, 2016.)*

Amgen appealed the district court's ruling to the US Court of Appeals for the Federal Circuit, which dismissed the appeal in an Aug. 10 opinion. The court noted that Amgen did not include any of its cell-culture patents on the list of patents it believed a claim of patent infringement could reasonably be made, nor did it bring suit on any of these patents. The court said Amgen could have done so and Hospira then would have had to respond with detailed statements as to why the patents are invalid, unenforceable or would not be infringed.

"In this scenario, Amgen would have had an opportunity to assess the reasonableness of its litigation position long before filing suit and being exposed to Rule 11 sanctions or antitrust liability," the appeals court said.

Landmon said this case is significant in that innovator companies won't be able to force discovery unless they are actively litigating the patents at issue. The decision "makes it a little more difficult for reference product sponsors," he said.

CYLTEZO'S COMPETITIVE STRATEGIES

Like Amgen's Amjevita, Cyltezo is approved for seven of the 10 indications on Humira's label: rheumatoid arthritis; juvenile idiopathic arthritis; psoriatic arthritis; ankylosing spondylitis; adult Crohn's disease; ulcerative colitis; and plaque psoriasis. It is not approved for pediatric Crohn's disease, hidradenitis suppurativa, or uveitis, which are still protected by orphan exclusivity.

FDA's Cyltezo approval letter notes that BI has a postmarketing commitment to "develop a comprehensive and robust control strategy to control for effector function of BI 695501." Submission of the final report is due August 2018.

Boehringer has said that while its main trial demonstrates equivalence in rheumatoid arthritis, it is gathering additional data on the biosimilar's use in Crohn's disease and psoriasis to support extrapolation of the biosimilarity data to other indications for which Humira is approved and to "increase the confidence in biosimilars." *(Also see "Boehringer Ingelheim Limbering Up With Humira Biosimilar" - Scrip, 14 Jun, 2017.)*

BI recently disclosed that it had begun a study to determine whether Cyltezo is interchangeable with Humira. The company said the study is the first in the US to investigate interchangeability with a Humira biosimilar candidate. *(Also see "Humira Biosimilar Interchangeability: The Race Begins" - Pink Sheet, 30 Jul, 2017.)*

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FDA Accelerates Inspection Process With New Concept Of Operations

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Now that US FDA has aligned its facility and product review organizations, the agency is launching new workflows outlined in a "concept of operations" agreement to accelerate work in those organizations, the heads of facilities and drug review organizations told staff in an Aug. 21 email.

The agreement is at the heart of efforts to speed up facility reviews in line with product reviews, which have accelerated because of user fee commitments.

Other efforts include encouraging firms to submit facility information early. *(Also see "ANDA Sponsors Get Wide-Open Facility Deadline For Priority Review" - Pink Sheet, 23 Aug, 2017.)*

In recent years, more and more drug marketing applications have been derailed by manufacturing facility GMP issues that hadn't been identified and resolved before user fee act review deadlines. *(Also see "Keeping Track Of CRLs: US FDA Again Faults Bausch + Lomb Manufacturing" - Pink Sheet, 11 Aug, 2017.) (Also see "Pfizer's EPO Biosimilar Stalls In US On Hospira Compliance Woes" - Pink Sheet, 22 Jun, 2017.)* The new workflows could help future applications avoid this fate.

The concept of operations agreement "will make review and inspection hopefully occur at the same time," Michael Kopcha, who heads the agency's Office of Pharmaceutical Quality, told an International Society for Pharmaceutical Engineering quality conference June 5, the day before the agreement was signed.

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> The agreement will help FDA meet a new commitment to tell generic drug firms how the agency has classified their facilities within 90 days of inspection.

A 90-DAY COMMITMENT

The concept of operations agreement will help FDA meet a new commitment to tell generic drug firms how the agency has classified their facilities within 90 days of inspection, according to the internal email from Janet Woodcock, director of FDA's Center for Drug Evaluation and Research, and Melinda Plaisier, associate commissioner for regulatory affairs.

The agreement goes further, applying the accelerated classification to brand drugs as well.

FDA classifies inspected facilities based on the severity of problems seen: no action indicated (NAI) if there are no problems; voluntary action indicated (VAI) if there are minor observations described in a Form 483 report that the firm can be expected to resolve on its own; and official action indicated (OAI) if the problems described in a Form 483 report are so serious that they warrant FDA issuing a warning letter or taking other steps such as seeking an injunction or referring the matter to the Justice Department for criminal enforcement.

Generics firms had asked for earlier notification so that if FDA has a problem with a facility, they would have time to fix it or switch to a different facility within the framework of marketing application approval timelines.

FDA has committed to achieving the 90-day facility classification goal by October 2018 under Generic Drug User Fee Amendments II.

The agency plans to achieve the goal much sooner by putting its new concept of operations into effect by this fall, the email said.

Under the concept of operations, the 90-day timeline would apply to nearly all drugs, the email said. The agreement does not cover compounded or investigational drugs. *(Also see "FDA Will Soon Begin Alerting Generics Firms To Facility Compliance Status" - Pink Sheet, 26 Jul, 2017.)*

A BROAD APPLICABILITY

The concept of operations agreement applies to pre- and post-approval, surveillance and for-cause inspections of human drug manufacturing facilities in the US and abroad.

The agreement will help by "ensuring consistency, efficiency and transparency in facility evaluations, inspections and regulatory decision-making for marketing applications across FDA," Woodcock and Plaisier said in the email.

They added that it would:

- Create clear roles and responsibilities across ORA and CDER functional units;
- Improve the agency's operational capacity by enhancing collaboration among offices;

- Enhance the quality and internal availability of information about inspection and review decisions; and
- Improve timelines for meeting user fee commitments and taking regulatory, advisory and enforcement actions.

The new concept of operations complements the reorganization of FDA's Office of Regulatory Affairs in May, which aligns field staff with CDER and the agency's other centers. It outlines how the reorganized offices will work together. *(Also see "FDA Aligns New Pharmaceutical Inspectorate Into Six Divisions" - Pink Sheet, 16 May, 2017.)*

PRE-APPROVAL EVALUATIONS

- The agreement spells out how FDA will gauge the readiness of facilities named in marketing applications.
- First CDER will lead pre-approval facility evaluations, with ORA participating, to decide whether an inspection is needed to support approvability of a marketing application from a quality perspective.
- The document notes that the agency will develop standard operating procedures to define ORA's and CDER's roles in this process.
- Upon submission of a marketing application, FDA will form an integrated quality assessment (IQA) team to provide quality recommendations that are supposed to be aligned, patient-focused and risk-based.
- These quality recommendations are to cover the drug substance, the drug product, the manufacturing process and the facilities.
- An application technical lead will head the IQA team and a regulatory business project manager will manage it.
- An assessor from the Office of Process and Facilities, or OPF, will perform an initial facility risk assessment based on information in the application and a site dossier from the Office of Surveillance, or OS. OPF and OS are the CDER Office of Pharmaceutical Quality.
- The assessor consults with the IQA team and various offices as appropriate to decide whether a site inspection is needed and if so, what are the areas of concern.

PRE-APPROVAL INSPECTIONS

- If an inspection is needed, ORA will conduct the inspection with CDER participating.
- An ORA investigator will lead the inspection, which may focus on the concerns raised by the IQA team. With the help of an inspection team, the ORA investigator will document any findings in a Form 483 report.
- The inspection team will provide an establishment inspection report to the IQA team after the director of ORA's investigations branch reviews it.
- The IQA team will address any outstanding issues through regulatory meetings with the applicant, or by issuing information request, discipline review or complete response letters, and by providing application approvability recommendations. The OPF assessor evaluates responses to the letters and provides overall approvability recommendations.

POST-APPROVAL FACILITY INSPECTIONS

- There also are product-specific post-approval facility inspections that mainly focus on process validation and manufacturing changes to ensure that commercial-scale processes conform to application commitments and GMP requirements.
- If critical issues are found, it is possible for these inspections to expand into surveillance inspections

SURVEILLANCE FACILITY INSPECTIONS

- Periodic system-based surveillance inspections focus on facilities rather than specific products.
- CDER's Office of Surveillance uses a surveillance risk model to decide which facilities to inspect. The model generates an annual risk-based ranking of sites.
- ORA leads these inspections with CDER participation, if requested.

SITE DOSSIER PROGRAM

- Prior to each inspection, the Office of Surveillance will prepare a site dossier that includes inspection history, recalls, shortages, customer complaints, foreign regulators' inspection outcomes, information from field alert reports and biological product defect reports, as well as quality metrics data, if available.
- The concept of operations document notes that periodic stakeholder analysis of the site dossier program will determine its extent of use.

THE POST-INSPECTION TIMELINE

- At the end of a surveillance inspection, the investigator will document the findings, issue the firm a Form 483 report and discuss it with the firm at the close of the inspection.
- If official action may be indicated, ORA must inform CDER within two days by entering that information into its Panorama software system.
- The concept of operations white paper gives ORA 45 days after the end of the inspection to complete an establishment inspection report, or EIR, and classify the facility as official action indicated, voluntary action indicated or no action indicated, in accordance with Field Management Directive 86.
- The white paper notes that CDER will, with input from ORA, develop guidance on possible follow-up actions based on inspection findings and other relevant information.

WHEN OFFICIAL, VOLUNTARY OR NO ACTION IS INDICATED

If ORA had initially indicated an OAI finding was likely, it would refer the matter to the Office of Manufacturing Quality, or OMQ, during the initial 45-day post-inspection period, also providing a

written classification analysis and electronic documents. OMQ is in the CDER Office of Compliance.

During a second 45-day period, OMQ would, after considering input from the Office of Chief Counsel, make a final classification and issue a decisional letter to the firm within 90 days post-inspection.

If the final classification is OAI, OMQ either by itself or in collaboration with ORA, would take an appropriate enforcement action within three months.

If OMQ downgrades the classification to voluntary or no action indicated, it would provide a written explanation in 40 days, leaving the Office of Compliance at least five days to issue a Field Management Directive 145 decisional letter within 90 days of inspection close.

If voluntary or no action is indicated at inspection close, ORA would not refer the matter to OMQ, and would instead be responsible for issuing an FMD-145 decisional letter within 90 days.

POST-INSPECTION SURVEILLANCE ANALYSIS

The Office of Surveillance in CDER's Office of Pharmaceutical Quality will conduct post-classification trend analyses. For example, it may identify a subset of firms that have worrisome quality trends for follow-up engagement, which it would carry out in collaboration with ORA.

The Office of Surveillance might focus on facilities that were reclassified from OAI to VAI. It might consider factors such as post-approval change history, quality metrics data if available, and drug shortage potential in deciding whether to pursue follow-up engagements such as written requests for information or in-person meetings.

FOR-CAUSE INSPECTIONS

ORA and the offices for process and facilities, surveillance and compliance can initiate a for-cause inspection by preparing an assignment per Field Management Directive 17.

ORA will take the lead on for-cause inspections – those involving new registrants or information that brings compliance into question. CDER may participate when appropriate.

If objectional conditions are seen, the firm will receive a Form 483 report at inspection close. Within 45 days, ORA will provide an establishment inspection report. The initiating office will have another 45 days to complete final classification, involving other offices as appropriate. All follow-up actions are to be completed within six months of the inspection.

PROCEDURAL REVISIONS LIKELY

The agreed upon concept of operations will likely spur revisions to various documents that spell out operational details for agency staff.

These would include the agency's Investigations Operations Manual, Manuals of Policies and Procedures, Compliance Program Guidance Manuals and the Regulatory Procedures Manual.

NO MORE EXCUSES

If the concept of operations document achieves its objectives, most inspection-released activities will be completed either 45 or 90 days post-inspection, and warning letters, if warranted, will be publicly posted within six months.

This would likely sit well with FDA officials who would no longer have to explain why it can take a year or more for warning letters to hit the street. *(Also see "FDA Promises Shorter, Quicker Drug GMP Warning Letters" - Pink Sheet, 30 Jun, 2016.))*

From the editors of the Gold Sheet. Published online August 27, 2017

REGULATORY UPDATE

UK Life Science Strategy Urges Continued Regulatory, Research Ties With EU

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The Life Sciences Industrial Strategy unveiled by Professor Sir John Bell on Aug. 30 contains a host of ideas on how to build up the £64bn sector into a "global hub" that will attract inward investment in a wide range of areas, and provide a "fertile environment" in which life sciences companies can flourish.

The strategy paints a picture of a UK science base supported by increased public funding where industry collaborates more closely with the National Health Service to speed up the adoption of new, innovative drugs. Digital innovation hubs will produce valuable real-world data, while streamlined processes for assessing new products will accelerate access to market.

Investments will be made in the manufacture and export of high-value products, with the help of grants and loans combined with regional incentives. In the research area, the UK will aim to increase the number of clinical trials carried out there by 50% over five years, with a focus on novel trial design.

Provision is made for the creation of more life science clusters and new UK companies valued at more than £20bn over the next ten years. In addition, the UK will aspire to "attract 2,000 new discovery scientists from around the globe" and to become an "international benchmark for success." A new Healthcare Advanced Research Program (HARP) would be set up through which industries, charities and the NHS could collaborate on "ambitious" and long-term UK-based projects.

Behind the recommendations in the strategy however, lies the spectre of Brexit

and the concerns of stakeholders about the negative effects it could have on the sector in areas such as regulation, research, freedom of movement, inward investment, and so on. Brexit was in fact one of the drivers behind the report, which suggests some ways of addressing these concerns, including retaining many of the current arrangements the UK has with the EU.

For example, the report says the UK and its Medicines and Healthcare products Regulatory Agency should "seek to continue to work closely with the EMA [European Medicines Agency] to deliver the best regulatory service for patients across the EU and UK."

It also suggests that the EU and the UK should try to continue working together in pharmacovigilance and clinical trials, and says that in the pre-competitive research area the UK "should also seek to continue to be involved in Europe's Innovative Medicines Initiative."

BROAD INDUSTRY REPRESENTATION

The industrial strategy is the result of a review of the long-term future of the industry led by Sir John, Regius Chair of Medicine at the University of Oxford and chairman of the Office for the Strategic Coordination of Health Research, and by the Life Sciences Industrial Strategy Board, which has broad representation from across the sector.

A range of stakeholders had input into the strategy, including global companies such as AstraZeneca, Johnson and Johnson, MSD, GSK, and healthcare groups, as well as SMEs and charities. It was commissioned as part of the Industrial Strategy Green Paper published in January this year. Unsurprisingly, given the close industry involvement in its development, companies have given the strategy a warm welcome.

Steve Bates, CEO of the BioIndustry Association and a member of the Life Sciences Industrial Strategy Board, said it was "fantastic to see the publication of a life sciences industrial strategy that can act as a springboard to an early sector deal for the life sciences industry." Bates noted that the BIA has long called for a revived industrial strategy to maintain and build

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> A range of stakeholders had input into the strategy, including global pharma companies and smaller firms, and it received a warm welcome from industry.

investment into the UK and grow the UK's innovative bioscience companies.

In an interview with the *Pink Sheet*'s sister publication *Scrip*, Mene Pangalos, executive vice-president of AstraZeneca's innovative medicines and early development biotech unit, said it was "nice to see a coherent plan that brings all of the components of the life sciences together to create a visionary and exciting strategy that will drive growth and prosperity in the UK in the future." *(Also see "AZ Chief Scientist Wants Britain To Be Like Boston" - Scrip, 30 Aug, 2017.)*

From the charity side, Sir Harpal Kumar, chief executive of Cancer Research UK, said: "With our impending exit from the EU and the NHS facing challenges on many fronts, this strategy comes at a critical time for the UK. We have a strong history of medical research in the UK and it's vital that we remain a world-class destination for the benefit of our economy and, most importantly, patients." He added, however, that it was "crucial there is sufficient government investment and commitment from the NHS to make it a reality as quickly as possible."

RETAINING LIFE SCIENCE SKILLS

Among other things the strategy highlights the danger of losing retaining skills in the sector – another Brexit-related risk raised by industry and other stakeholders. Noting that the "ultimate success of the Life Sciences Industrial Strategy is closely tied to the ability to train and recruit the best possible workforce, equipped with a breadth of critical skills," the strategy cautions that the "potential disruption associated with Brexit could lead to some loss of talent from the sector."

The UK, it says, is highly dependent on a steady influx of international scientists, and forecasts suggest that science sectors will cumulatively require 180,000 to 260,000 people by 2025. Around 26% of academic staff in UK universities are non-UK nationals; in STEM (science, technology, engineering and mathematics), 13% are from outside the EU and 17% from within.

"This talent underpins the science base in universities, the growth of high-tech companies in the sector, the effectiveness of the NHS in delivering healthcare and the large companies contributing to life sciences within the UK," says the strategy, adding that it will be important to create "an opportunity to bring very high-level talent into the country over the next five years."

The "ultimate success of the Life Sciences Industrial Strategy is closely tied to the ability to train and recruit the best possible workforce, equipped with a breadth of critical skills.")

From the editors of Scrip Regulatory Affairs. Published online August 31, 2017

Parties Vie For Place At EMA's First Ever Public Hearing On Medicines Safety

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The European Medicines Agency is busy analyzing the applications it has received from people interested in attending its first ever public hearing on the safety of marketed medicines that is scheduled to take place on Sept. 26, and which will focus on valproate-containing medicines.

The deadline for members of the public to register their interest in attending the event ended on Aug. 25. The EMA said the feedback it had received so far was "very positive" and that the application process had drawn "many expressions of interest from all target groups."

"We are currently analyzing the applications received in order to select the speakers and observers who will be invited to join the public hearing," a spokesperson for the agency told the *Pink Sheet*. The EMA will select participants based on their experience with valproate-containing medicines.

"The selection will also seek to accommodate as many people as possible but reflecting an appropriate representation of all groups of stakeholders, with a focus on patients and practitioners," the spokesperson added. Pharmaceutical companies were also allowed apply to speak at the hearing.

As the selection process for speakers and observers is still ongoing, the spokesperson told the *Pink Sheet* that it preferred not to comment further at this stage on the number of applications received or who had applied to attend the event. Applicants are to be told within two weeks after the application deadline whether they can attend the event in person. The event will also be broadcasted live on the agency's website.

The EMA waited a long time to select an appropriate topic for its first public hearing. Public hearings are mandated under the EU pharmacovigilance legislation, which came into force on July 2012. In March this year, the agency decided to get public input on the use of the anti-epileptic drug valproate in women and girls who are pregnant or of childbearing age. *(Also see "EMA Picks Valproate For First Public Hearing On Safety Of Marketed Medicines" - Pink Sheet, 13 Mar, 2017.)(Also see "Valproate In The Spotlight As EMA Releases Date For First Ever Public Hearing" - Pink Sheet, 12 Jun, 2017.)*

To ensure that the discussions at the hearing are as focused as possible, the EMA's pharmacovigilance committee, PRAC, in July released three questions for potential speakers. *(Also see "EMA Poses Three Questions For the Public Ahead Of Valproate Hearing" - Pink Sheet, 11 Jul, 2017.)* When deciding on the speakers at the hearing, the EMA will look at, among other things, how the applicants plan to address these questions.

SURVEY ON VALPROATE RISKS DURING PREGNANCY

The public hearing has generated much interest, especially among affected patient groups. The UK-based Epilepsy Society, for example, has re-launched its survey that was initially announced last year to ascertain the awareness levels among women of the potential risks of sodium valproate if taken during pregnancy. The society is hoping to present the survey findings at the hearing.

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"Last year's survey showed that 20 per cent of women who were taking sodium valproate were not aware that it could cause harm to a developing baby during pregnancy. And 27 per cent had not had a discussion led by their healthcare professional about the risks," said Nicola Swanborough, content manager at the Epilepsy Society.

Also last year, the UK medicines regulator MHRA had launched a toolkit to promote greater awareness of guidelines about the drug to both patients and healthcare professionals. The society has re-launched the survey 18 months later to see if the statistics delivered by the first survey have changed. "We want to see whether the [MHRA's] toolkit and its important messages are reaching the right people," Swanborough told the *Pink Sheet*. The survey will remain open until Sept. 26.

The survey is being undertaken with the charities Epilepsy Action and Young Epilepsy "and we will be making a joint presentation [of the survey results] at the EMA public hearing," Swanborough said. The society hopes that the EMA hearing "will give a voice" to the thousands of women across the world whose babies have been affected by sodium valproate.

"We hope that correct measures can be put in place to ensure that in the future all women will be made aware of the risks around the medication so that they can make an informed decision about their treatment with their doctor. For some women, sodium valproate may be the only drug that will control their seizures, and convulsive seizures can pose risks for a woman and her baby during pregnancy. The benefits have to be assessed against the risk to the mother and baby," she added.

From the editors of Scrip Regulatory Affairs. Published online August 30, 2017

Colombian Crack Down On Compulsory Licensing Under Attack

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Civil society groups in Colombia have signed a letter calling for the Colombian government to repeal a decree that they say stifles compulsory licensing and prevents declarations of interest (DPIs) from being used to control medicine prices. According to the groups, the decree, published by the ministry of commerce, is to punish the health ministry for slashing the price of **Novartis AG**'s cancer drug Glivec (imatinib) after declaring it to be of public interest.

The ministry of commerce published decree 670 of 2017 in April. The decree changes the procedures for declaring the existence of reasons for why a product may be of public interest. It also stipulates that representatives from the ministry of commerce and the national planning department should sit on the technical committee that makes recommendations on whether there is a case for public interest.

The decree came not long after the ministry of health issued a declaration of public interest for Glivec in June 2016 *(Also see "Colombia v Novartis: Do Big Prices Mean More Compulsory Licensing?" - Scrip, 10 Jun, 2016.)*. Usually a DPI is a step towards issuing a compulsory license, which would allow generic competition. But in this instance the ministry cut the price of Glivec by 44% from 368 pesos (US$0.12) per mg to 206 ($0.07) pesos.

The move was unpopular with industry. Novartis challenged the DPI *(Also see "Novartis Takes On Colombia Over Glivec Pricing" - Scrip, 22 Dec, 2016.)* "Novartis believes that the circumstances surrounding the DPI for Glivec could create a damaging precedent that could be applied to other patent-covered treatments in Colombia and other countries. At a stroke, this could destroy intellectual property – one of the fundamental frameworks the biomedical research sector relies on for its existence," said the company at the time.

AFIDRO, the pharmaceutical industry lobby group launched its own law suit against the health ministry and subsequent price regulations, claiming that a declaration of public interest should not be used for anything other than a compulsory license. *(Also see "Colombia's Glivec Pricing Means "Worst Of Scenarios" For Pharma Industry" - Pink Sheet, 30 Dec, 2016.)*

In their letter, published on July 28, the NGOs claim that the decree was "punishment" for the Glivec DPI and price cut, which they said followed extensive pressure from Novartis and AFIDRO. According to the groups, the decree erroneously considers the only objective of a DPI to be to issue a compulsory license. However, the objective of a DPI is actually much wider and is to decide whether protecting a particular right, like IP rights, is in the collective interest. They also claim there is no justification for changing the composition of the technical committee, particularly with representatives from the ministry of commerce, whose main priorities are international trade, not public health.

> A recent decree says that representatives from the ministry of commerce and the national planning department should sit on the panel that reviews drugs of potential public interest.

IMPACT

Pressure had been mounting for the health ministry to declare new hepatitis C treatments to be of public interest and many NGOs were calling for compulsory licenses to bring the cost of treatment down. However, Colombian authorities instead opted to win price reductions through a Pan American Health Organization-backed joint procurement exercise that brought big savings for Gilead Sciences Inc.'s Harvoni (sofosbuvir plus ledispavir) and a combination of Bristol-Myers Squibb Co.'s Daklinza (daclatasvir) and Gilead's Sovaldi (sofosbuvir), *(Also see "Colombia Celebrates Massive Hep C Price Fall Thanks to Joint Procurement" - Pink Sheet, 24 Aug, 2017.)*. In a press conference health minister Alejandro Gaviria said that authorities would be unable to take steps to introduce generic competition because the drugs were covered by patents.

The organizations behind the letter are Misión Salud, Federación Médica Colombiana, Observatorio del Medicamento de la Federación Médica Colombiana (OBSERVAMED), Fundación Ifarma, Centro de Información de Medicamentos de la Universidad Nacional de Colombia (CIMUN) and Comité de Veeduría y Cooperación en Salud.

From the editors of Scrip Regulatory Affairs. Published online August 25, 2017

India's Rx Policy Shifts Could Spark Turf Wars Within Government

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India's draft pharmaceutical policy 2017 appears to contradict itself in critical areas and blur established roles, stoking dissent even within government constituents, while also adding to the turbulence in the sector. The new GST (goods and services tax) regime in India, pricing pressure in the US and manufacturing compliance-related complexities are among the key challenges that the Indian industry is already grappling with.

The Pink Sheet highlights five proposals in the draft policy, put out by India's department of pharmaceuticals (DoP), that have stirred a hornet's nest and are expected to make the proposed Aug. 30 meeting of certain stakeholders and various ministries rather engaging.

TWO DISTINCT AGENCIES

In the area of drug price regulation, the draft policy stipulates that the "Government shall not be the regulator and the regulator shall not be the Government"; they would be two distinct agencies. Yet, subsequent statements suggest that prices once fixed by India's pricing regulator, the National Pharmaceutical Pricing Authority (NPPA), shall not be revised by NPPA "unless directed specifically by the government or a higher court to do so." While India's department of pharmaceuticals does currently consider price-related appeals from industry, the new draft appears to confer more absolute powers.

A top government functionary told the Pink Sheet that the draft's explanation clearly runs counter to its own policy statement and alleges that entire exercise appears aimed at regulating the regulator, undermining its very role. Industry, on the other hand, claims that some of the measures could rein in the pricing body's recent elevated "activism." The pricing regulator and industry have rarely been on the same page and tensions have escalated over the recent past with both sides generally sticking to their guns. *(Also see "India's Pricing Tussle Escalates After Regulator Names "Overcharging" Firms" - Pink Sheet, 12 Apr, 2017.)*

REGULATOR – STRENGTHENED OR DILUTED?

The policy draft suggests that the NPPA will be strengthened and assisted by an advisory body for pricing, nominated by the government. The panel is expected to comprise physicians, pharmacists, other experts and representatives from civil society, industry, and government. While advise of this body will be "recommendatory" and the NPPA may accept or modify the advice rendered, the pricing authority will need to "assign reasons in writing for doing so." A regulatory expert told the Pink Sheet that the diverse advisory panel could likely pull in different directions and claims that the exercise in effect aims to dilute the regulator's role. It could also pose tricky questions when it comes to inherent conflicts of interest, in addition to posing further delays and complexities in decision-making.

Some industry experts, however, underscore that the NPPA itself has outlived its utility. "It should be replaced by a model similar to the NICE (National Institute of Health and Care Excellence) of the UK. The pricing models of NICE are decided on the principles of pharmacoeconomics, which does not focus on costs alone but on the ratio of cost to benefit and the value it adds to the patient," Ajit Dangi, president and CEO of Danssen Consulting and a former director general of the Organization of Pharmaceutical Producers of India (OPPI), which represents foreign firms in the country, said.

Dangi, a former president and executive director of Johnson &Johnson India, believes that the current Indian pricing policy is "not sound" and "dis-incentivizes" a good quality manufacturer.

PREPARING INDIA'S NATIONAL LIST OF ESSENTIAL MEDICINES

The draft also appears keen to give control to the department of pharmaceuticals, which falls under India's ministry of chemicals and fertilizers, to decide on India's National List of Essential Medicines (NLEM). Drugs on the NLEM are subject to price caps in India and this list has traditionally been drawn up by a committee constituted under the aegis of India's Ministry of Health and Family Welfare. The new draft, though, stipulates that "the department of pharmaceuticals will prepare the list of medicines for price regulation and transmit them to the NPPA for fixing the price ceilings." Expectedly, the health ministry has not taken kindly to this power shift and reports suggest that it will oppose the proposal strongly.

PRICE CAPS ON ALL STRENGTHS/DOSAGE FORMS

The policy draft also notes that Schedule I of India's Drug Prices Control Order (DPCO) – this schedule essentially comprises the latest NLEM (currently the 2015 version) – will contain only the medicine's name without referring to their strength and dosage forms. It elaborates that "all strengths and dosage forms" of that medicine shall be

liable for price caps. Drug firms claims that could imply that even combinations, which include drugs not on the NLEM, can attract price caps. In addition, there is the worrying reference of "ceiling prices" for selected drugs rather than retail prices. Industry experts told the Pink Sheet that these proposals could expand the span of price control on medicines in India significantly and also diffuse the lines between "scheduled [drugs on the NLEM] and non-scheduled drugs [those outside the NLEM]."

The core committee report pertaining to drawing up NLEM 2015 had earlier noted that the essentiality of a medicine had been considered in terms of its dosage form and strength too. It, however, clarified that any dosage form of a medicine, other than the dosage form included in NLEM, but in the "same strength and route of administration, which does not have significant difference in terms of pharmacokinetics/ pharmacodynamics/ efficacy-safety profile over the dosage form mentioned in the list" will be considered as included. But, in general, fixed dose combinations were not included unless the combination has a "unequivocally proven advantage" over individual ingredients administered separately, in terms of increasing efficacy, reducing adverse effects, or improving compliance.

WITHIN THE AMBIT OF ONE DEPARTMENT

The latest policy draft, circulated by India's department of pharmaceuticals (DoP), also reignites the prickly debate on the need to converge or at least place under the same umbrella various departments dealing in healthcare and pharmaceuticals, for effective delivery of healthcare services.

The latest policy draft suggests that all the regulators/commissions pertaining to the pharmaceutical industry will be brought within the ambit of one department to ensure accessibility and affordability of drugs, ease of doing business and "more coordinated synergies." If this means shifting India's Central Drugs Standards Control Organization (CDSCO) out of the purview of India's health ministry, then the health ministry does not seem to be keen to relent any time soon. Both the DoP and the NPPA currently fall under the ambit of the ministry of chemicals and fertilizers.

Ironically, an Indian parliamentary standing committee on commerce had in 2013 suggested that the DoP be "subsumed" within the health ministry. The committee had then said that on occasions it found the DoP and the department of health and family welfare to be on "different wavelengths" on issues of public health.

"Since medicines are an integral aspect of public health structure, the department of pharmaceuticals may be subsumed within the Ministry of Health and Family Welfare for effective policy formulation and monitoring of pharma sector in larger public interest," the committee had recommended at the time. *(Also see "Indian blanket brownfield ban call brings fresh headwinds for FDI" - Scrip, 14 Aug, 2013.)*

From the editors of PharmAsia News. Published online August 28, 2017

Amarin Seeks ITC Action Against Products 'Cloaked' As Dietary Supplements

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Two years after successfully suing the US FDA to enable communications about the off-label use of *Vascepa* (icosapent ethyl), **Amarin Corp. PLC** is again seeking an unusual route in trying to protect its market for the triglyceride-lowering agent – by asking the International Trade Commission (ITC) to block unapproved drugs "cloaked" as dietary supplements.

Amarin is requesting an ITC investigation "into the unlawful importation or sale" in the US of synthetically produced omega-3 products that are predominantly composed of eicosapentaenoic acid (EPA) in either ethyl ester (EE) or re-esterified (rTG) form "and are falsely labeled, and/or promoted for use as, or in 'dietary supplements,'" the company said in an Aug. 30 complaint.

The filing names as proposed respondents 18 companies that supply, manufacture or market ingredients used in, or finished formulations of, synthetically produced omega-3 products that are alleged to have been falsely labeled and promoted as dietary supplements.

These products do not meet the federal Food, Drug and Cosmetic Act's (FDCA) definition of "dietary supplement" and are actually unapproved "new drugs" under the statute, the complaint states, alleging that their importation, sale and marketing constitutes unfair trade practices and unfair methods of competition.

Filed under Section 337 of the Tariff Act, the complaint requests ITC institute an investigation of the companies' importation and sale of synthetically produced omega-3 products. Amarin also seeks a permanent general exclusion order barring entry of synthetically produced omega-3 products into the US and a permanent limited exclusion order specifically directed at each of the companies named in the complaint.

> The ITC "gives us an opportunity o exclude the illegal articles that are being imported by the defendants we're suing, but the general exclusion order would also apply to other similar products."
> – King and Spalding's Dwyer

GOING AFTER THOSE WHOSE DON'T 'PLAY BY THE RULES'

In an interview with the *Pink Sheet*, Amarin's attorneys said the action is aimed at protecting the company's competitive interests for Vascepa, a synthetically produced, ethyl ester form of EPA approved in July 2012 to reduce triglyceride levels in adults with severe hypertriglyceridemia.

Joseph Kennedy, Amarin's executive vice president and general counsel, said the complaint seeks to exclude companies from the market who are not playing by the rules. Although Amarin could have sued the named firms in court for unfair trade practices, "we saw in the ITC an efficient and narrowly targeted way to achieve the goal."

"The International Trade Commission gives us an opportunity to exclude the illegal articles that are being imported by the defendants we're suing, but the general exclusion order would also apply to other similar products," said Lisa Dwyer, a partner in King and Spalding's FDA and life sciences practice and an attorney for Amarin. "It's a way to allow a remedy against a dispersed commercial environment. When there are a lot of players out there and it's hard to identify them specifically, it's a way to address the entire class."

In bringing the action, Amarin is making the argument that violating FD&C Act standards constitutes unfair trade practices under the Tariff Act, Dwyer said.

She suggested the action could have important ramifications for other pharmaceutical companies because if Amarin prevails, Sec. 337 of the Tariff Act could "become a new potent tool for competitors to use to make sure that everyone is playing by the rules."

AGGRESSIVE LEGAL STRATEGY

The ITC action marks another step in Amarin's novel and aggressive legal strategy to protect and boost sales of Vascepa, its first FDA-approved product.

The company has been stymied in its efforts to significantly broaden the drug's labeling to include adults on statin therapy with high triglyceride levels. Amarin's supplemental new drug application to expand the indication on the basis of the ANCHOR study results resulted in an April 2015 complete response letter, with FDA requesting the company provide evidence of a reduction in cardiovascular risk.

Amarin is conducting a CV outcomes trial, REDUCE-IT, in 8,175 patients who have elevated triglyceride levels and other CV risk factors despite stabilized statin therapy. Results from the trial are expected in the second or third quarter of 2018.

In the meantime, however, Amarin sued FDA in May 2015 challenging the agency's regulations on off-label drug promotion and seeking a determination that it could communicate about the ANCHOR study results with healthcare providers.

In that lawsuit, Amarin argued that FDA has permitted dietary supplement manufacturers to make claims that their omega-3 fatty acid products "may" reduce the risk of coronary heart disease and that EPA "lowers triglycerides," while simultaneously forbidding Amarin from telling doctors that Vascepa lowered triglycerides for patients with persistently high levels in the ANCHOR trial. *(Also see "Off-Label Litigation: Amarin Sues FDA In Bid To Promote Vascepa Fish Oil" - Pink Sheet, 7 May, 2015.)*

In August 2015, a federal judge ruled that 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 court also endorsed a package of statements, materials and disclosures for Amarin's use in its communications with healthcare providers. *(Also see "Off-Label Unleashed? Amarin Win Suggests Firms Still Need Strong Data To Skirt FDA" - Pink Sheet, 7 Aug, 2015.)*

FDA and Amarin ultimately settled the litigation, and the agreement included an optional preclearance process for the company's future communications about off-label use of Vascepa. *(Also see "Off-Label Promotion Settlement Includes Optional Preclearance Process" - Pink Sheet, 8 Mar, 2016.)*

18 COMPANIES TARGETED

Amarin's ITC complaint asserts that a large majority of omega-3 products imported or sold in the US are legally marketed dietary supplements consisting of common fish oil, which typically includes a mixture of saturated and unsaturated fats. Common fish oil is not synthetically produced and includes omega-3 fatty acids in their natural triglyceride form, the complaint states.

The company is not seeking ITC scrutiny of such products, "nor is Amarin requesting an investigation into synthetically produced omega-3 products in EE or rTG form that are not predominantly comprised of the omega-3 acid EPA," the company said.

Rather, the company is targeting the importation and sale of products containing purified EPA or omega-3 fatty acid mixtures that are predominantly EPA in the ethyl ester form or in the re-esterified form. The complaint names as proposed respondents 18 companies that sell synthetically produced omega-3 oil, or encapsulated synthetically produced omega-3 oil, for use in or as finished products marketed as dietary supplements. *(See box.)*

The complaint notes that in addition to Vascepa, there are FDA-approved branded and generic drugs on the market that contain omega-3 mixtures in their ethyl ester form, such as **GlaxoSmithKline PLC**'s *Lovaza* (omega-3-acid ethyl esters).

"Since the launch of these FDA-approved drugs, companies have been increasingly falsely labeling and promoting products that contain chemically heightened levels of EPA as 'dietary supple-

18 PROPOSED RESPONDENTS

- Royal DSM NV and corporate affiliates DSM Marine Lipids Peru S.A.C., DSM Nutritional Products and DSM Nutritional Products Canada Inc.
- Ultimate Biopharma (Zhongshan) Corp.
- Marine Ingredients AS and related company Marine Ingredients LLC
- Golden Omega S.A. and related company Golden Omega USA LLC
- Nordic Pharma Inc.
- Croda Europe Ltd. and related company Croda Inc.
- Tecnologica de Alimentos S.A.
- Nature's Bounty
- Nordic Naturals
- Pharmavite LLC
- Innovix Pharma Inc.
- J.R. Carlson Laboratories Inc.

ments,'" the complaint states.

However, these synthetically produced omega-3 products do not bear or contain a "dietary ingredient " and are otherwise excluded from the FD&C Act's definition of a dietary supplement, the complaint states. Amarin additionally asserts that such products are unapproved new drugs under the statute.

BRAND DAMAGE AND LOST SALES

Labeling and promoting such products as dietary supplements "is unfair to Amarin and other pharmaceutical companies that have invested the necessary resources to bring competing drug products to market, and it serves as a disincentive for drug companies to invest resources in drug development in the future," the complaint states. In addition, the proposed respondents have been able to "avoid the drug approval process and the associated time and investment necessary to conduct clinical trials to show that their products are safe and effective for each intended use and to obtain FDA approval for each intended use."

The importation and sale of synthetically produced products has damaged the Vascepa brand by exploiting its status as an FDA-approved drug and led to losses in sales and market share for Amarin's drug, resulting in lost profits and price erosion, the complaint asserts.

Amarin has not yet reached profitability on Vascepa sales and "anticipates incurring losses for an indefinite period of time," the complaint states. Vascepa net product revenues based on sales to distributors totaled $79.3m during the six months ended June 30, 2017. "Amarin's revenues would have been higher but for the proposed respondents' unfair acts and unfair methods of competition," the filing maintains.

The complaint describes Amarin's current investment behind Vascepa, including a 150-person sales force in addition to at least 250 sales representatives provided through a co-promotion agreement with **Kowa Pharmaceuticals America Inc.** The company said it expects total costs of conducting the REDUCE-IT trial to exceed $200m.

16-MONTH TIMELINE FOR AN ITC INVESTIGATION

Amarin attorney Jeffrey Telep, a partner in King and Spalding's international trade practice, said the commission has 30 days to decide whether or not to institute an investigation as requested by Amarin, although that time period can be extended.

If an investigation is triggered, the commission will assign the case to an administrative law judge (ALJ), who will establish a target date for completion of the investigation. Target dates typically run to about 16 months, during which there is a trial, an ALJ decision and a final commission determination, Telep said. The US president has 60 days to review the commission's decision, but action at that level is rare.

Dwyer said one of the reasons Amarin is looking for an expedited resolution through the ITC process is because the ongoing REDUCE-IT trial, if successful, could change the treatment paradigm for CV risk reduction in patients with high triglycerides.

Amarin filed the ITC complaint "to protect its commercial interests now and to make sure that patients don't get fooled or sidetracked by products that are sold as quick fixes for complex disease states," she said.

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OTC, Supplement Co-Packaging Potential Could Be Clipped By FDA Proposed Rule

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An FDA proposed rule that deems dietary supplements unapproved drugs when co-packaged with pharmaceutical products could put firms like **Innovus Pharmaceuticals Inc.** in an enforcement bullseye if made final in its current form.

Innovus in July launched tandem sales of its *Apeaz* OTC pain relief topical and its *ArthriVarx* joint health supplement, with both products sold together though physically packaged together.

Innovus CEO Bassam Damaj said the San Diego firm, which commercializes OTC drugs and other consumer products for men's and women's health, vitality and respiratory diseases, is testing the market for supplements and OTCs sold together. "We're looking to see how it's going to perform," Damaj said in an interview.

FDA's Center for Drug Evaluation and Research says that under the currently proposed rule, the agency would determine on a case-by-case basis whether co-packaged nonprescription drugs and vitamin, mineral or supplement products already available in the US are in violation of agency policy. The agency published the proposed rule in December 2015, and in its latest regulatory agenda update, which is non-binding, sets an October 2018 target date for publishing a final rule.

"It is difficult to respond to questions about hypothetical scenarios, particularly where the outcome is rather fact-dependent/fact specific. Depending on the specific facts and circumstances, a dietary supplement co-packaged with an OTC drug could suggest or imply that the dietary supplement is intended for a drug use and would, therefore, be considered a drug under" FDA regulations, said Tralisa Colby, a public affairs specialist in CDER's Office of Communications.

However, the proposed rule – "Fixed-Combination and Co-Packaged Drugs: Applications for Approval and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter Monograph" – doesn't allow exemptions for supplements that are sold as part of a single package with a drug.

Innovus Pharmaceuticals offers its Apeaz topical analgesic OTC only in tandem sales with its ArthriVarx joint health supplement.

CRN believes any proposals on co-packaging supplements and OTC drugs should be a separate conversation.

"When used as part of a fixed-combination or co-packaged drug, dietary supplements are considered to be an active ingredient in that product and subject to the requirements of this proposed rule," CDER said in the proposed rule.

In a footnote clarifying its thinking in the proposal rule, CDER said it considers "dietary supplements that are combined into a single dosage form with, or co-packaged with, a drug to meet the definition of 'drug' under" FDA regulations. The center also stated in the footnote that the "proposed rule does not otherwise address nor affect FDA policy on dietary supplements."

However, the overall language of the proposal rule – docket FDA-2015-N-1260 – indicates it would affect the supplement industry. Moreover, the industry perceives the definition of dietary supplements as drugs when co-packagesas short-sighted and unfair.

Drug manufacturers also are concerned that the proposed rule would curtailing their marketing strategy of offering multiple OTC products with similar or different indications in a single package.

A DRUG REGULATION FOR SUPPLEMENT MARKETING?

The Council for Responsible Nutrition let FDA know about its concerns in May 2016 comments on the proposed rule.

"FDA was ostensibly putting out a proposed rule around drugs and we saw them referencing supplements. We dropped [comments] into the agency just to remind them that that, 'Hey this is not supposed to be a conversation about supplements. If you want to have that, you should have that separately, but not in the context of this drug rule,'" said Steven Mister, president and CEO of the supplements trade group..

FDA previously has compelled firms that were combining drug and dietary supplements in a single formulation to cease making and marketing the products, enforcement that met little push-back. *(Also see "Bayer Warning Letters Reinforce FDA Ban On Supplement/Drug Combinations" - Pink Sheet, 3 Nov, 2008.)*

But offering separate supplement and drug products in a single package differs from combining supplement and drug ingredients in a single formulation, industry says.

Mister suggests FDA seems to be on thin regulatory ice to include vitamins, minerals and supplements in the proposed drug co-packaging rule. "It says that a dietary supplement becomes a drug by virtue of being

packaged with a drug."

"Now we are moving from just not putting the ingredients in the same pill to where FDA seems to be saying, 'Well, you can't even co-package them together.' We don't see anything in [FDA regulations] that prohibits that," he said in an interview.

"We're saying, 'This is not the place to have that conversation, FDA. If you want to have it then you should have a conversation separately about the co-packaging of supplements with a drug.'"

DISTINGUISHING SUPPLEMENT FROM MEDICINE?

Part of FDA's concerns about co-packaging a supplement and a drug is that consumers could confuse the products' doses and directions, perhaps using the drug product indefinitely as most supplements are used, or using a supplement at the dosage indicated for the co-packaged drug.

That isn't a potential problem with Innovus' Apeaz OTC and ArthriVarx supplement, Damaj said. "The topical product is completely different and it is not in the same box as Apeaz," he said.

Although dissimilar in delivery format, the topical drug and the oral supplement provide complementary benefits, which is why Innovus is offering them together only. "When somebody orders Apeaz, they get it with the supplement," Damaj said.

Apeaz is an OTC topical analgesic monograph compliant drug for arthritis pain relief containing– camphor 4%, menthol 10% and methyl salicylate 30% – that also contains excipient ingredients that are common as active ingredients in joint health supplements, methyl-sulfonyl methane (MSM) and glucosamine sulfate.

"There are no other products that contain those five ingredients at those concentrations and tested in the collagen arthritis model showing efficacy," Damaj said.

According to its label, Apeaz is indicated for temporary relief of minor aches and pains of muscles and joints associated with simple backache, arthritis, strains, bruises and sprains.

Innovus says ArthriVarx's "two main ingredients" are the herb andrographolide paniculate and hyaluronic acid in a formulation "designed to maximize joint health."

Part of FDA's concern is that consumers could confuse the products' doses and directions.

SALES DRIVER FOR FIRMS ...

Including a vitamin, mineral or supplement product that complements the indicated effect of a nonprescription drug available in a single package, as Innovus is doing with Apeaz and ArthriVarx, could have appeal as a sales driver.

That is an option CRN wants FDA to allow the industry. "We could foresee that somebody might want to have supplements and an OTC medicine that are shrink-wrapped together," Mister said.

While a tandem offering with a topical drug and an oral supplement might appear as easier for users to distinguish between the two products, CRN expects it is not asking too much of consumers to correctly follow dose and usage directions for co-packaged oral delivery drugs and supplements.

"What I think consumers are smart enough to know is that if it has a Supplement Facts box on it, it's a supplement, and if it has a Drug Facts box on it, it's a drug," Mister said.

"If you have two products that are co-packaged and they each have their own labeling consumer can figure out that one is a supplement and one is a drug."

... CONVENIENCE FOR CONSUMERS

In addition to consumers correctly distinguishing packages of nutritionals from drugs, trends in nonprescription drug use support allowing co-packaging the products.

"What's happening at the same time is you're seeing more and more OTC medicines that are meant for either a chronic condition or you're taking them every single day," Mister said.

For instance, consumers using daily OTC allergy remedies and omega-3s or herbals daily would appreciate the convenience of the drug and supplements being available together.

"Why couldn't the manufacturer whose making both of those products co-package them for consumer convenience?" Mister said, adding, "Even if it's not on the condition [indicated for the OTC], it's just convenient to have them all packaged together."

Innovus' Apeaz and ArthriVarx offering is gauging consumer regard for the convenience of supplements and drugs sold together. "So far the response has been great. We've been shipping a lot of orders," Damaj said.

Innovus markets a total of 25 consumer health products, including OTC topicals for premature ejaculation prevention and hemorrhoid treatment and supplements for prostate health, bladder control and sexual health. It also expects FDA approval this year for its abbreviated new drug application filed in 2015 for a fluticasone proportionate spray intranasal corticosteroid, a generic of **GlaxoSmithKline Consumer Healthcare LP**'s *Flonase Allergy Relief*. *(Also see "Fluticasone Spray Competition Grows With Perrigo Launch Of West-Ward Product" - Pink Sheet, 6 Jun, 2016.)*

In 2016, Innovus closed its $630,000 acquisition of brands from Beyond Human LLC, a firm known for its testosterone booster supplement *Beyond T Human* and its natural human growth agent *HGA*. *(Also see "Industry Roundup: Supplement Labeling Guide Corrected, Nu Skin Settles" - Rose Sheet, 7 Mar, 2016.)*

More recently, Innovus in June gained a license for exclusive rights to the University of Iowa Research Foundation's US patent application on use of thymol and carvacrol (monoterpene phenols) for induction of increased skeletal muscle endurance, lean muscle mass and reduced adiposity. The monoterpene phenols are considered generally recognized as safe by FDA for use in dietary supplements and conventional foods and beverages. *(Also see "Tech Transfer Roundup: Janssen, Eisai, Apexian, Innovus And More" - Scrip, 11 Jul, 2017.)*

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Drug Co-Packaging Proposed Rule Could Hamper Some OTC Marketing

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FDA should narrow its proposed definition of "co-packaged" drugs to avoid curtailing OTC firms' marketing strategy of offering multiple products with similar or different indications in a single package, say industry stakeholders.

A proposed rule published in December 2015 – "Fixed-Combination and Co-Packaged Drugs: Applications for Approval and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter Monograph," docket FDA-2015-N-1260 – would extend FDA regulations on Rx fixed-combination drugs to products with prescription and nonprescription ingredients, co-packaged drugs and combinations of active ingredients under consideration for inclusion in an OTC monograph.

The proposal also states that dietary supplements co-packaged with OTC drugs would be considered unapproved new drugs because they are sold with a drug product. While the proposed rule has been pending for quite some time, the issue is getting renewed attention as the OTC/supplement co-packaging strategy is an emerging sales driver for firms in both industries and is raising questions on how FDA might enforce the proposal if made final.

For OTC drugs, packages with containers of both daytime and nighttime formulations of the same ingredient could be deemed mislabeled under the proposed rule, as well as co-packaged products with little similarity in use, such as an oral analgesic sold in tandem with a topical pain relief product.

The Consumer Healthcare Products Association says the proposal could render common offerings of two or more separate OTCs in a single package as mislabeled if the products are not intended to be used together, according to the trade group's March 2016 comments to FDA's Center for Drug Evaluation and Research.

Reckitt Benckiser's Mucinex Sinus-Max and Bayer's Alka-Seltzer Plus offerings with day and night formulations in a single package could be mislabeled under an FDA proposed rule on co-packaging.

> CHPA said Kochanowski explained that because "'co-packaged' has multiple meanings outside of the regulatory environment," and thus FDA's proposal could have unintended consequences.

"We disagree that shrink wrapping absent labeling such as 'convenience' or 'value pack' is an implied claim that the products are intended to use used together," wrote Barbara Kochanowski, the trade group's regulatory and scientific affairs vice president.

Kochanowski explained that because "'co-packaged' has multiple meanings outside of the regulatory environment," CHPA is "concerned that this proposed rule, unless much more clearly clarified regarding exemptions, may have unintended consequences and cause regulatory uncertainty for manufacturers and retailers."

Kochanowski pointed out that other marketing terms used for self-care products sold together include "family pack, bonus pack, convenience pack, free sample, first aid," and "there could be many other terms used in the future that are also acceptable but not clearly" defined as compliant and not subject to the proposed rule.

CHPA suggests CDER define a co-packaged drug as "a product that contains two or more separate drugs in their final dosage forms that are intended to be used together at the same time for a common or related therapeutic purpose, labeled as such, and that are contained in a single package or unit."

Bayer AG, manufacturer of OTC products including the *Alka-Seltzer* lines and the *Aspirin* brand, also suggested in March 2016 comments that CDER refine its definition for co-package. The proposed definition "is overly broad and could lead to consumer confusion," wrote Todd Paporello, vice president and head North American regulatory affairs pharmaceuticals and consumer health at Bayer's Whippany, N.J., office.

CDER should modify the definition by adding to "intended to be used together" the phrase "as evidenced by their labeling

for use for the same indication in the same population," Paporello said. The qualifying phrase would exclude from FDA's "co-packaged drug" definition products with labeling that "does not treat the same symptoms in the same population."

"Consumers see and are familiar with a variety of product packaging that is currently on the market that has samples or other unrelated items attached. Regardless of whether labeled with 'value', 'convenience' or other similar words, it is clear from their labeling that the products are not intended or implied to be used together," he added.

Additionally, Paporella noted co-packaging for daytime and nighttime formulations of the same product should be considered compliant with FDA labeling regulations. "There is nothing in the labeling of day and night products that suggests or states that the products are to be used together simply because they are co-packaged together. Regardless of whether a product is intended for use during the day or night, the product has to have labeling for the safe and efficacious use of the product," he stated.

In its most recent but non-buiding update to its regulatory agenda, FDA estimated it would issue a final rule in October 2018. Response to the proposal promoted FDA to extend the comment period in early 2016. *(Also see "Industry Roundup: DXM Bill Moves, CHPA Biz Dev VP, Neurobrands Injunction" - Rose Sheet, 25 Apr, 2016.)*

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FDA's NDA And BLA Approvals: Kymriah, Vabomere, Cyltezo

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				
Chemo Research	Benznidazole	Treatment of Chagas disease (American trypanosomiasis), caused by Trypanosoma cruzi, in pediatric patients 2 to 12 years of age.	P, 1	8/29/2017
Remplex (The Medicines Co.)	*Vabomere* (meropem/ vaborbactam)	Treatment of patients 18 years of age and older with complicated Urinary Tract Infections (cUTI), including pyelonephritis	P, 1, 4	8/29/2017
Teva	*Austedo* (deutetrabenazine)	Treatment of tardive dyskinesia.	P, 9	8/30/2017
New Biologics				
Boehringer Ingelheim	*Cyltezo* (adalimumab-adbm)	Biosimilar to Abbvie's *Humira* approved for several indications including rheumatoid arthritis, psoriatic arthritis, adult Crohn's disease and ulcerative colitis.		8/25/2017
Novartis	*Kymriah* (tisagenlecleucel)	CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.		8/30/2017

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

Generic User Fee Hikes Could Disrupt US FDA Drug Pricing Campaign

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New user fees could reverse efforts by the US FDA to increase generic drug availability and push drug prices down.

The agency announced the generic drug user fees for fiscal year 2018, the first year of GDUFA II, in a Federal Register notice scheduled to be published Aug. 29. They include several new charges, including one based on ANDA ownership, called the program fee. *(Also see "ANDA Holder Fee Will Start With Industry-Driven Database 'Clean-Up'" - Pink Sheet, 22 Oct, 2016.)*

Program fees are tiered based on the number of ANDAs a firm owns, in part to limit the burden on small businesses. Firms owning one to five ANDAs must pay $159,079. Those owning six to 19 ANDAs will pay $636,317 and firms owning 20 or more ANDAs will pay $1.59m. (*See table.*)

When calculating the fee, FDA said it factored in the fact that firms may withdraw ANDAs upon finding out how much it will cost them. The agency called it "potential portfolio adjustment," i.e. "applicants may choose to withdraw some of their approved ANDAs in order to move to a lower tier and reduce their fee exposure."

Such an effect could hurt FDA efforts to deal with problems with drug price increases.

Indeed, because many generics have narrow margins, the program fee could make some products no longer profitable, force a withdrawal and reduce the number of manufacturers of some products. With fewer competitors, there would be less pressure on price, potentially allowing some to increase.

The agency has implemented new policies intended to push some generics to the market faster, including a new priority review pathway as part of GDUFA II. *(Also see "FDA Drug Pricing Policy Offers Short-Term PR Gain, More Long-Term Actual Benefit" - Pink Sheet, 27 Jun, 2017.)* Commissioner Scott Gottlieb has made the issue one of his priorities since taking office in May. *(Also see "Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff" - Pink Sheet, 16 May, 2017.)*

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HUNDREDS OF FIRMS IN POSITION FOR 'PORTFOLIO ADJUSTMENT'

FDA said in the notice that it identified 339 companies in the small business tier, 74 applicants in the medium size tier and 65 in the large company tier.

However, it appears that agency officials are expecting a significant amount of changes now that fees are known, including firms withdrawing or selling all their ANDAs. After factoring in portfolio adjustment, as well as changes for inactive and unclaimed ANDAs, the agency calculated the fees assuming the small business tier would have 258 firms, the medium size tier would have 52 firms, and the large firm tier would have 62 firms, according to the notice. It is a decrease of 106 firms, 22.2%, across all tiers.

The most recent ANDA ownership list included 183 firms that owned only one ANDA and 78 that owned two. Some of those firms may be willing to sell or withdraw their ANDAs to avoid paying the fee.

Sixteen firms owned six ANDAs, meaning they could save $477,238 by dropping one ANDA and moving from the medium size business to the small business tier.

Another two owned 20 ANDAs, according to the list. If they withdrew or sold one ANDA, they could drop from the large tier to the medium tier and save $954,475.

John DiLoreto, executive director of the Society of Chemical Manufacturers and Affiliates' Bulk Pharmaceuticals Task Force, said in an interview that he thought the ANDA listings may be ripe for change, in part because many firms did not know how many ANDAs FDA said they owned.

The agency attempted to verify the owners of all the approved ANDAs in its database over several months once the GDUFA II agreement was completed. But more than 1,900 ANDAs were not claimed, which likely complicated program fee calculations. *(Also see "Generic Industry Consolidating But Still Mysterious" - Pink Sheet, 7 Jun, 2017.)*

FDA ran into a similar problem when GDUFA I launched in 2013. The agency asked manufacturers to self-identify their facilities so an accurate fee for active pharmaceutical and finished dosage form facilities could be calculated. But the fee calculated the first year was much higher than expected, in part because fewer facilities registered. *(Also see "GDUFA Facility Fees*

Will Be Significantly Higher Than Expected" - Pink Sheet, 16 Jan, 2013.)

APPLICATION FEES JUMP; IS A SUBMISSION RUSH COMING?

FDA now is depending on applications rather than facilities to carry the bulk of the user fee revenue burden.

The agency expects GDUFA II to generate $493.6m in FY 2018, which is 53% more than the $323m generated in FY 2017. Of the revenue that must be generated in FY 2018, 35% will come from program fees and 33% will come from ANDA fees.

As a result, application fees are skyrocketing. The cost of filing an ANDA will be $171,823 in FY 2018, a 144% increase from FY 2017. The calculation was based on an estimate that the agency will receive 948 full application equivalents during the fiscal year, which includes ANDAs that are filed, as well as those refused to be received or withdrawn, which incur a partial or full refund.

The submission estimateis less than FDA already has received in FY 2017. *(Also see "FDA's Generic Approvals Catch A Bit Of Breath In July But Continue At Fast Pace" - Pink Sheet, 7 Aug, 2017.)*

To avoid paying a much higher fee in October, sponsors may rush to submit ANDAs in September, although it may be difficult to complete applications with only four weeks' notice. FY 2017 already has seen several submission rushes for a variety of reasons. *(Also see "Generic Drug Puzzle: Why Did ANDA Submissions Spike Again?" - Pink Sheet, 11 Apr, 2017.)*

NOT MUCH STICKER SHOCK

There did not appear to be much sticker shock among industry groups in reaction to the fee announcement.

Lisa Parks, VP of sciences and regulatory affairs for the Association for Accessible Medicines, which helped negotiate GDUFA II while known as the Generic Pharmaceutical Association, said in a statement that the "fees are in line" with what was anticipated.

In GDUFA I, facility fees constituted 70%, while ANDA fees were 24%, of the annual revenue total. *(Also see "GDUFA: Fee Avoidance Affects Rates Again" - Pink Sheet, 12 Aug, 2013.)*

Facility fees will vary under the new fee schedule, even though they will constitute substantially less of the overall revenue.

Domestic API manufacturers will pay $45,367 in FY 2018, a 2.6% increase from FY 2017. Domestic finished dosage form facilities will pay $211,087, which is an 18.4% decrease from FY 2017. Foreign manufacturers will pay an extra $15,000 to cover FDA's costs for overseas inspections.

DiLoreto said the facility fees came out to about what had been expected, which was close to the FY 2017 rate.

Facility fees were a source of tension among many industry stakeholders throughout GDUFA I, in part because it was believed the high rates kept small firms from entering the generic market. *(Also see "Generic User Fees Need Small Business Waiver, Firms Say; Congress May Agree" - Pink Sheet, 24 Jun, 2013.)*

Contract manufacturers will pay a separate fee in FY 2018: $70,362 for domestic firms and $85,362 for foreign firms.

The fee was based on 71 domestic CMOs and 97 foreign CMOs. Gil Roth, president of the Pharma and Biopharma Outsourcing Association, which helped negotiate GDUFA II, said the figures were about what was expected.

CMOs pay one-third of a finished dosage form facility fee in GDUFA II. *(Also see "Generic Drug User Fees Will Jump More Than 50% In FY 2018" - Pink Sheet, 16 Oct, 2016.)*

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FY 2018 Generic Drug User Fees

LEGACY GDUFA FEES	FY 2017	FY 2018	CHANGE
ANDA	$70,480	$171,823	$101,343 (144%)
Prior Approval Supplement*	$35,240	$0	$35,240 (-100%)
Drug Master File	$51,140	$47,829	-$3,311 (-6.5%)
Domestic Active Pharmaceutical Ingredient Facility	$44,234	$45,367	$1,133 (2.6%)
Foreign Active Pharmaceutical Ingredient Facility	$59,234	$60,367	$1,133 (1.9%)
Domestic Finished Dosage Form Facility	$258,646	$211,087	-$47,559 (-18.4%)
Foreign Finished Dosage Form Facility	$273,646	$226,087	-$47,559 (-17.4%)

NEW GDUFA II FEES	AMOUNT
Domestic Contract Manufacturing Organization	$70,362
Foreign Contract Manufacturing Organization	$85,362
Program Fee-Large size operation generic drug applicant	$1,590,792
Program Fee-Medium size operation generic drug applicant	$636,317
Program Fee-Small business operation generic drug applicant	$159,079

*Prior approval supplement fees were eliminated in GDUFA II.

The new generic drug program fee will cost small and large businesses alike a substantial amount of money in fiscal year 2018. Application fees also will skyrocket as GDUFA moves to depend on applications, rather than facilities, for revenue.

Source: Federal Register notice

Spark Therapeutics' Vision Loss Gene Therapy Gets FDA Panel Review

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Spark Therapeutics Inc.'s *Luxturna* (voretigene neparvovec) gene therapy is going through one of the last regulatory hurdles to approval as an FDA advisory committee is scheduled to review the company's biologics license application on Oct. 12.

In July, Spark announced that FDA had accepted the BLA for one-time treatment of vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy under a priority review designation. Designated as a breakthrough therapy for a rare pediatric disease, voretigene neparvovec, with the proposed trade name of Luxturna, has a Jan. 12, 2018 user fee goal. *(Also see "Keeping Track Of Novel Agents: US FDA Approves Nerlynx And Vosevi, Turns Down Evenity; Macrilen Returns" - Pink Sheet, 23 Jul, 2017.)*

FDA announced that its Cellular, Tissue, and Gene Therapies Advisory Committee would review the BLA in a Federal Register notice to be published Aug. 28.

Luxturna is the first gene therapy application to be filed in the US. The filing is based on two open-label Phase I trials in patients who received the therapy between 2007 and 2012 and a Phase III trial in patients who were treated between 2013 and 2015. The clinical trial program included 41 participants with vision loss, age four to 44.

THERAPY IMPROVED FUNCTIONAL VISION

Results of the randomized, controlled, open-label Phase III clinical trial were published In The Lancet in July. The study found that voretigene neparvovec improved functional vision, light sensitivity and visual field in study participants with RPE65-mediated inherited retinal disease (IRD). Spark noted in a release that a natural history study has shown that people with the disease eventually progress to complete blindness.

Participants were randomly assigned to intervention (n=21) or control (n=10); one participant from each group withdrew before intervention, leaving 20 intervention and nine control participants. The study found a statistically significant and clinically meaningful difference between intervention and control participants at one year, per the clinical trial's primary endpoint, mean bilateral multi-luminance mobility testing (MLMT) change score (difference of 1.6; 95% CI, 0.72, 2.41; p=0.0013).

MLMT evaluates functional vision by documenting the participants' ability to navigate a mobility course under a variety of specified light levels ranging from one lux (the equivalent of a moonless summer night) to 400 lux (the equivalent of an office environment).

The company said participants maintained the functional gains observed 30 days post-administration at the one-year primary endpoint. There were also statistically significant improvements in two secondary endpoints, including full-field light sensitivity threshold testing averaged over both eyes. Spark said a third secondary endpoint, the change in visual acuity averaged over both eyes, was not statistically significant between intervention and control participants.

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A Phase III clinical trial found that voretigene neparvovec improved functional vision, light sensitivity and visual field in study participants with RPE65-mediated inherited retinal disease (IRD).

An additional endpoint using the Goldmann III4e test stimulus to measure the visual field area of the original intervention group showed significant improvement (p=0.0059), nearly doubling at year one, while a slight decrease was observed in the control group over the same period.

The company reported that no serious adverse events associated with the therapy or deleterious immune responses were observed. Most ocular events were mild with the most common being transient mild ocular inflammation, transient elevated intraocular pressure, cataracts and interoperative retinal tears.

Spark has not indicated how it will price its therapy but analysts have projected the cost could reach $1m when both eyes are treated. *(Also see "Gene Therapy Reimbursement: Is Blindness A Bad First Test?" - Pink Sheet, 29 Jun, 2017.)*

The Institute for Clinical and Economic Review is conducting a value assessment of voretigene neparvovec, with a draft report expected for November.

The Institute for Clinical and Economic Review is conducting a value assessment of voretigene neparvovec to help payers develop policies for covering the drug. A report assessing the comparative clinical effectiveness and value of the therapy is expected from ICER by January 2018, with a draft report scheduled for November. *(Also see "ICER Eyes Gene Therapy: Category-wide Policy In Works As Spark Moves To Approval" - Pink Sheet, 5 Jul, 2017.)*

GENE THERAPY FORERUNNER IN EUROPE

In July, Spark submitted a marketing authorization application for Luxturna to the European Medicines Agency for treatment of patients with vision loss due to Leber congenital amaurosis or retinitis pigmentosa caused by confirmed biallelic RPE65 mutations. *(Also see "Spark Therapeutics' Vision Loss Gene Therapy Heads For EU Market" - Scrip, 3 Aug, 2017.)*

Inherited retinal diseases are a group of rare blinding conditions caused by one of more than 220 different genes. Spark noted that people living with IRD due to biallelic RPE65 gene mutations often experience night blindness due to decreased light sensitivity in childhood or early adulthood and involuntary back-and-forth eye movement. As the disease progresses, individuals may have loss in their peripheral vision and may also loose central vision, becoming totally blind.

While Spark is on track to launch the first gene therapy in the US, **uniQure NV** was the first to get a gene therapy approved in Europe. Its *Glybera* (alipogene tiparvovec) received EU approval in 2012 for an ultra-small indication, familial lipoprotein lipase deficiency. It is priced at $1.4m but only one patient was ever treated with the therapy commercially. The company decided not to renew the drug's marketing authorization, which is to expire in October, citing the small indication and use restrictions. *(Also see "White Flag Raised: UniQure Gives Up On Glybera, But Not Gene Therapies" - Scrip, 21 Apr, 2017.)*

Spark was founded in Philadelphia in March 2013. Luxturna is the gene therapy company's lead product candidate. It has three other products in the pipeline: SPK-7001 in a Phase I/II trial for choroideremia; SPK-9001, which is being developed in collaboration with **Pfizer Inc.**, in a Phase I/II trial for hemophilia B; and SPK-8011, in a Phase I/II trial for hemophilia A.

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Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Current practice and benefit/risk considerations for use of prescription opioid products containing hydrocodone or codeine for the treatment of cough in pediatric patients	Pediatric	Sept. 11
Pediatric-focused safety reviews, as mandated by the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, for various products	Pediatric	Sept. 12
GlaxoSmithKline's zoster vaccine recombinant, adjuvanted	Vaccines and Related Biological Products	Sept. 13
Results from a clinical study of Purdue Pharma's *Butrans* (buprenorphine) transdermal system in patients ages 7-16 years old for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate	Anesthetic and Analgesic Drug Products/Drug Safety and Risk Management	Sept. 14
Pfizer's *Sutent* (sunitinib) for adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma following nephrectomy	Oncologic Drugs	Sept. 19
PTC Therapeutics' *Translarna* (ataluren oral suspension) for treatment of patients with dystrophinopathy due to a nonsense mutation in the dystrophin gene	Peripheral and Central Nervous System Drugs	Sept. 28
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
Discussion of patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for drugs intended to treat interstitial cystitis and bladder pain syndrome. Also discussion of whether bladder pain syndrome and interstitial cystitis reflect overlapping or different populations, and whether it is appropriate to assess efficacy in the same way for both conditions	Bone, Reproductive and Urologic Drugs	Dec. 7

Pink Sheet

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