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REMS BARRIERS: US FDA Takes 'Foundational Step' To Improve Generic Access

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US FDA Commissioner Scott Gottlieb is keeping a spotlight on the agency's efforts to curb brand company abuses of the Risk Evaluation and Mitigation Strategy (REMS) system that block generic entry.

In a Nov. 8 statement announcing FDA's release of a draft guidance for use of a single drug master file in a shared REMS submission, Gottlieb took the opportunity to emphasize that FDA is exploring new steps to reduce the likelihood that branded drug companies can use the existence of REMS to slow the entry of generic competition. Specifically, he said the agency is considering allowing generic drug applicants to request a waiver from the requirement that they use a shared REMS with the innovator company.

The draft guidance, "Use of A Drug Master File for Shared System REMS Submissions," recommends how applicants can submit collective sets of files to FDA that represent all participating firms.

"My hope is that the use of a standardized process for collecting information in the new REMS document template will help streamline the drafting and review of shared system REMS making it easier for companies to engage in a shared REMS," Gottlieb stated. "Today's action is a foundational step toward reforms we may implement in the near future."

"My message is this: end the shenanigans" – FDA Commissioner Gottlieb

The statement coincided with Gottlieb's appearance at a Federal Trade Commission workshop on competition in prescription drug markets, at which he reiterated his concern about branded companies who "game" the system by taking advantage of rules or exploiting loopholes to delay generic approval. He cited the branded companies use of REMS to prevent generic firms from acquiring doses of branded drugs to conduct bioequivalence studies as an example.

Gottlieb told the FTC workshop: "My message is this: end the shenanigans."

BYPASSING SHARED REMS

In his statement on REMS, Gottlieb noted that the agency will be providing information on how and when generic drug applicants can request a waiver from using a shared system REMS with the innovator company and the factors that FDA intends to consider.

The law currently requires branded and generic companies to reach agreement on the implementation of a single, shared REMS and any generic drug application referencing a branded drug with a REMS with elements to assure safe use (ETASU) must use a single, shared REMS with the innovator unless FDA waives the requirement.

Gottlieb said the agency knows that ne-

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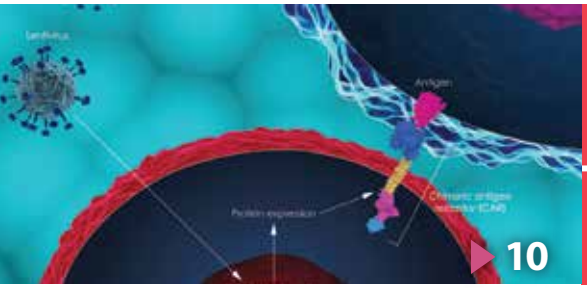

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gotiations to reach agreement on shared system REMS can take extended periods of time and block the timely entry of a generic competitor.

"A waiver would free generic entrants from the requirement that they reach agreement with a branded firm for a shared system REMS," he stated. "This can obviate the ability of branded sponsors to use these negotiations as a way to slow generic entry."

Gottlieb has previously raised the possibility of allowing generics to develop their own REMS in testimony at Congressional hearings. *(Also see "Brand Exclusivity 'Gaming' To Be Addressed At US FDA Meeting" - Pink Sheet, 25 May, 2017.)*

COLLABORATING WITH OTHER AGENCIES

Gottlieb has made it a priority to foster more robust generic competition since taking the helm of the agency in May. He has repeatedly criticized the tactics brand companies have used to block generic entry, including their use of REMS to deny generic companies' access to purchase branded drugs for use in bioequivalence studies. The issue was discussed at a public meeting in July on ensuring the Hatch-Waxman Act continues to balance access and innovation. *(Also see "FDA Exploring Whether Public Shaming Can Stop REMS Abuses" - Pink Sheet, 18 Jul, 2017.)*

Gottlieb addressed the topic again when he spoke at the National Press Club in Washington, DC. Nov. 3. He noted that it takes between 2,000 and 5,000 doses of a branded drug to run a bioequivalence study comparing the generic drug to the branded drug and that many generic companies have told FDA they cannot get access to the drugs to do these studies to file their applications.

"Oftentimes we see branded companies selling drugs through a tight supply chain. They might sell through a single specialty pharmacy with tight control of who the drug can be sold to."

"Oftentimes we see branded companies selling drugs through a tight supply chain. They might sell through a single specialty pharmacy with tight control of who the drug can be sold to," Gottlieb said. "I believe they have rules in place that make it difficult for the pharmacy or the distributor or whoever's handling the drug to actually make the sale to a generic company, or a sale in bulk fashion to a generic company."

Gottlieb noted that brand activities do not always fall within the purview of FDA and that he is willing to think of ways to collaborate with other agencies to address this.

ALLOWING PURCHASE OF BRANDED DRUGS IN EUROPE

Gottlieb also noted that the agency has talked about potentially allowing generic companies to go to Europe to buy the branded drugs.

Asked what the Association for Accessible Medicines thinks about this idea, AAM President and CEO Chip Davis Jr. said the best option, and the one that AAM supports, is for Congress to pass legislation like the CREATES Act.

"Should that not happen, using non-US reference products as samples for bioequivalence testing might be an option, if FDA feels comfortable relying on such products as having been demonstrated to be the same as the reference product," Davis said. "Simply put, a large and diverse set of stakeholders have come to realize that the current gaming of the system needs to be rectified. As such, the FDA and the Administration should use whatever tools they have to their fullest extent."

The Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act, S. 974, would allow generic sponsors to sue innovators if a generic firm has obtained a covered product authorization from FDA and the brand company fails to provide "sufficient quantities" of the REMS-covered product. A similar bill introduced in the House, the Fair Access for Safe and Timely (FAST) Generics Act, H.R. 2051, would prohibit innovators from restricting access to covered products to eligible product developers for the purpose of avoiding generic competition.

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More ANDAs To Be Eligible For Priority Review, Gottlieb Says

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The US FDA is ready to again expand the cohort of ANDAs that could receive a priority review.

Commissioner Scott Gottlieb would not reveal the new categories of generic drugs to be made eligible for priority status, but said Nov. 6 they could be announced in the coming days. He told the Association for Accessible Medicines' Fall Tech Conference that the agency has the staff available to conduct more of the truncated reviews.

"We're still going to announce a couple of areas where we're going to try to give priority focus or prioritize certain applications over others," Gottlieb said. "I think that we have the resources to do it. I have raised this question with the OGD staff and they feel comfortable that we have the capacity."

Several application types already are eligible for the faster priority review under the generic drug user fee program and associated agency policy, which worried some in industry that the pathway could be damaged by opening it to too many ANDAs.

Gottlieb responded that the Office of Generic Drugs workload has not reached "a steady state" where too many applications have been prioritized and "everything falls into a priority bucket."

Under GDUFA II, which launched Oct. 1, ANDAs have two review paths. The standard review allows a first action within 10 months of filing and the priority review in eight months. *(Also see "ANDAs Can Get Priority, Eight-Month Reviews Under User Fee Deal" - Pink Sheet, 24 Sep, 2016.)*

A first action is an approval, tentative approval, complete response or refuse to receive action.

FDA created the priority review pathway in part to respond to concerns about rising drug costs. Stakeholders and members of Congress argued that allowing more generic competition on the market would create more pricing pressure. *(Also see "Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff" - Pink Sheet, 16 May, 2017.)*

WHICH PRODUCTS WILL BE ADDED TO PRIORITY REVIEW SCHEME?

Among the applications that can be prioritized are first generics, those that could mitigate a drug shortage, and applications part of the President's Emergency Plan for AIDS Relief.

In June, the agency announced that it would offer a priority review to applications where there are fewer than three ANDAs approved for the reference product. *(Also see "FDA Drug Pricing Policy Offers Short-Term PR Gain, More Long-Term Actual Benefit" - Pink Sheet, 27 Jun, 2017.)*

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It is possible that complex products could gain access to the priority pathway.

FDA has been encouraging entry of generics for so-called complex products, which traditionally have been difficult to develop because of problems copying the delivery device and other issues. The agency already has said it is considering adjusting some regulations around complex product equivalence, including instructions for use and device sameness. *(Also see "Generic Combination Products May Be Permitted Delivery Device Variations" - Pink Sheet, 4 Jun, 2017.)*

FDA also has been looking to spur competition for several drugs where patents and exclusivity have expired, but no generics have been approved, including some complex products. *(Also see "FDA's Off-Patent, Off-Exclusivity List Draws Few Takers Early On" - Pink Sheet, 4 Aug, 2017.)*

While priority review can be an advantage, it depends on a quality application being submitted to gain a faster approval. Sponsors also must send facility information two months before the ANDA is submitted so the agency can begin inspection planning. *(Also see "FDA Offers To Expedite 'Priority' ANDA Reviews By Previewing Facility Information" - Pink Sheet, 26 Jun, 2017.)*

DOES FDA ACTUALLY LEARN FROM MULTIPLE REVIEW CYCLES?

FDA also is determining whether the issues causing multiple ANDA review cycles are productive for the overall process.

Gottlieb said during the conference that during one of his previous stints at FDA, new drug sponsors were battling a

FIRST-CYCLE APPROVAL RATES

- **FY 2015:** 10.7%
- **FY 2016:** 14.3%
- **FY 2017:** 12.8%

Note: Data as of Oct. 1, 2017. Some figures could change depending on the outcome of pending applications.

Source: FDA presentation slides

similar issue and the agency determined that many of the additional review cycles were not necessary and did not lead to new learning.

Gottlieb said he wants the agency to "look hard at the reasons for that and make sure when applications do undergo multiple cycles, we're getting something for it." He added that more guidances and internal policy documents are expected to help systematize the ANDA review process.

Indeed, as of Oct. 1, the first-cycle approval rate for ANDAs submitted in the first three years of formal review goals (during GDUFA I) has not exceeded 15%. (*See box, p. 5.*)

OGD Director Kathleen Uhl said during the conference that the multiple review cycles are not a good use of FDA resources and that the current rate is behind the trend established during the life of the prescription drug user fee program, GDUFA's' older sibling.

Uhl said OGD is expected to benefit from prior experience and adapt faster.

"There's a lot of expectations out there that we will go from where we are now at the end of GDUFA I to something much better than that, and quickly," she said. "And the only way that's going to happen is together, FDA and industry."

Many applications require three or more review cycles for approval. While an improved first-cycle approval rate is desired, FDA also would like to cut the average number of review cycles needed to two, if possible. *(Also see "ANDA Reviews: First-Cycle Desired, But Two-Cycles OK?" - Pink Sheet, 27 Jul, 2015.)*

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FDA

Gottlieb Promotes 'Team' Work For Product Reviews

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US FDA Commissioner Scott Gottlieb intends to reorganize drug reviewers from multiple disciplines into teams that would handle a product's entire life-cycle, an attempt to break down the siloed nature of many areas within the agency.

In a Nov. 3 speech at the National Press Club, Gottlieb said agency experts that handle pre-market review also should remain involved during post-market monitoring. "[Our scientific officers] must have the stewardship over the products they evaluate that extends throughout the entire product life-cycle," he said. "The commitments that stir our efforts before a product is approved for use are equally important after it's made more widely available."

The reorganization appears related to Gottlieb's idea to create specialized groups that could help reviewers with complicated issues that they do not usually encounter. *(Also see "Gottlieb's FDA: Specialized Groups Could Create Review Consistency, Speed" - Pink Sheet, 23 Mar, 2017.)*

But it's also an idea that FDA officials have considered for some time. When the Office of Pharmaceutical Quality was created in 2015, it included a life-cycle group that its new drugs group gave products to after approval.

FDA also has wanted to create teams of reviewers that would handle all products in the same drug class and then transfer them to a team that would handle post-approval supplements and generics. *(Also see "Woodcock's Passion Project: CDER Chief Shifts Duties To Lead Quality Office" - Pink Sheet, 19 Jan, 2015.)*

US FDA Commissioner Scott Gottlieb

Gottlieb said his reorganization will place pre- and post-market experts on the same teams. He wants more collaboration, such as by encouraging experts to work directly with colleagues in other offices rather than request a formal consult, as often happens now.

He said the reorganization is intended to move the agency away from "a structure that had people working in discrete organizational units that often operated as independent entities" to one that allows reviewers "to take a more universal view of the products they evaluate."

Such a move could place surveillance and epidemiology staff with reviewers and other product-specific staff, itself potentially undoing a previous reorganization.

The Office of Surveillance and Epidemiology was made a separate entity to emphasize FDA's commitment to safety following the withdrawal of **Merck & Co. Inc.**'s COX-2 inhibitor *Vioxx*. *(Also see "CDER Reorganization Takes Effect, With Renamed Offices" - Pink Sheet, 15 May, 2006.)* But an Institute of Medicine report published in 2006 said there was resource imbalance between OSE and the Office of New Drugs. *(Also see "Sweeping Changes At CDER Recommended In IoM Drug Safety Report" - Pink Sheet, 22 Sep, 2006.)*

The team-based approach could be particularly useful in the review of combination products, which can require reviews by new drug as well as Center for Devices and Radiological Health staff. The often-slow process has been the subject of congressional and FDA streamlining efforts. *(Also see "Combo Product Review Pilot At US FDA Will Offer All Applications Intercenter Consults" - Pink Sheet, 20 Dec, 2016.)*

SINGLE REVIEW MEMO POSSIBLE FOR OND

Gottlieb said changes to the OND structure also are under consideration "to address how new science is changing the nature of

how new drugs are developed."

FDA launched an OND make-over following the departure of long-time director John Jenkins, spearheaded by Center for Drug Evaluation and Research Director Janet Woodcock. It includes making reviews more uniform between divisions. *(Also see "CDER Director Woodcock Plans Changes To Drug Reviews During OND Transition" - Pink Sheet, 6 Mar, 2017.)*

OND now is organized into the Offices of Drug Evaluation I-IV, as well as the Office of Antimicrobial Products and Office of Hematology and Oncology Products. NDAs upon filing flow to the various groups for review.

Gottlieb said OND also is piloting one common shared review memo that "will ensure early cross-disciplinary interaction among scientists and clinicians who have specialized knowledge in disease that inform product review."

"A single review memorandum will also be much more accessible to the biomedical research community," he added.

[*Editor's note: Gottlieb and Woodcock will both be speaking at the FDA/CMS Summit on Dec. 5. For more information, please visit the conference homepage.*]

MORE DISEASE-FOCUSED OFFICES PLANNED

Reorganization at the agency is not uncommon. Commissioner Margaret Hamburg in 2011 created a directorate system, including an Office of Medical Products and Tobacco to oversee drug, device and tobacco operations. *(Also see "FDA Reorganization Adds "Directorate" Layer, But Sharpens Agency's Focus" - Pink Sheet, 18 Jul, 2011.)*

Within CDER, Woodcock also has overseen several organizational changes, including the creation of OPQ and elevation and growth of the Office of Generic Drugs into a super office. *(Also see "Generic Drugs Gain Status Boost Within CDER" - Pink Sheet, 7 Sep, 2012.)*

Gottlieb also wants to create an Office of Patient Affairs as a central contact point for patient groups and advocates. *(Also see "US FDA's Centralized Patient Affairs Office Aims For No Disruption" - Pink Sheet, 13 Sep, 2017.)*

In addition, the 2016 21st Century Cures Act created the Oncology Center of Excellence at FDA, which centralized oncology resources across the agency. *(Also see "FDA's Oncology Center Of Excellence On Equal Terms With CDER In New Org Chart" - Pink Sheet, 28 Jul, 2017.)*

Gottlieb added during the speech that he planned more disease-focused offices at FDA to provide stakeholders a single point of contact.

There has been talk of creating additional centers of excellence, but FDA and stakeholders have warned that too much subdividing could create problems. *(Also see "Don't Rush To Reorganize FDA, McClellan Says" - Pink Sheet, 29 Feb, 2016.)*

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New UK Pathway To Cut Access Times For Breakthrough Products By Up To Four Years

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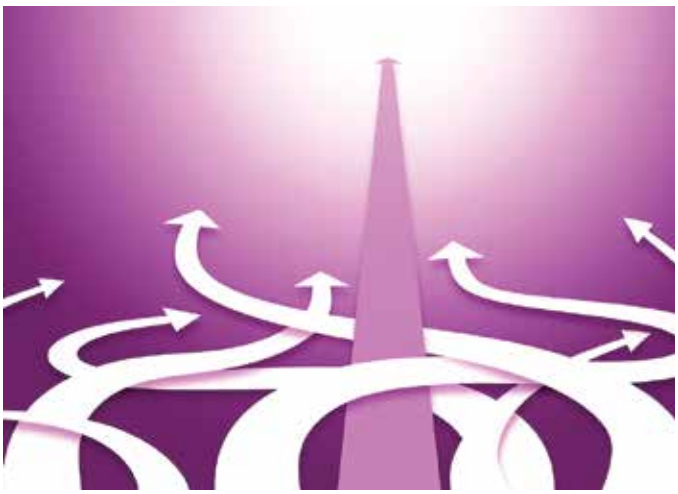
The UK government has backed the creation of an "accelerated access pathway" (AAP) under which a handful of selected breakthrough innovations – drugs, medical devices, diagnostics and digital products – could reach patients up to four years earlier than under standard assessment procedures.

The new pathway, to be introduced in April 2018, is expected to shorten the overall time to market for certain "transformative" new drugs in England, mainly by allowing cost-effectiveness evaluations to be carried out in tandem with the regulatory approval process. It will also offer companies early price negotiations and the potential for "flexible and confidential commercial arrangements."

Candidate products will be selected by a new "Accelerated Access Collaborative" chaired by former GlaxoSmithKline chief executive Sir Andrew Witty and comprising representatives of national regulatory and evaluation bodies, with input from industry, patients and clinicians. The AAC will be set up by the end of the year and the first products to enter the new pathway are expected to be identified from April 2018.

The government makes clear, though, that a commitment to faster access to what will no doubt be expensive new drugs must



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> Plans will "guarantee collaboration between the life sciences sector and the NHS post-Brexit – benefiting the economy and creating jobs"
> – Lord O'Shaughnessy

> "If the Review's ambition for innovation is to truly take hold then it requires both NHS buy-in and top-level government leadership" – BIA CEO Steve Bates

be balanced against the financial sustainability of the National Health Service. The new pathway, it says, must be "cost neutral" for the health service and "must deliver improved value to the taxpayer." To this end, a new strategic commercial unit will be established within NHS England to negotiate what the government calls "cost-effective deals"

The proposals are contained in the government's long-awaited response to the Accelerated Access Review (AAR), an independent report produced in October 2016 by Professor Sir John Bell and supported by the Wellcome Trust. In its response, the government broadly supports the proposals outlined in the AAR, which looked at ways of speeding up access to innovative new health technologies.

Health minister Lord O'Shaughnessy said the new arrangements would not only benefit patients but would "guarantee future collaboration between the life sciences sector and the NHS post-Brexit – benefiting the British economy and creating jobs."

Life science companies have been pushing for mechanisms to shorten times to market for innovative products and strengthen the life sciences sector, particularly as uncertainty mounts over the UK's relationship with the EU after Brexit in March 2019. The key AAR proposals were reiterated in the industry-led Life Sciences Industrial Strategy revealed on Aug. 30. *(Also see "UK Life Science Strategy Urges Adoption Of Accelerated Access Review, As Govt Prepares Response" - Pink Sheet, 7 Sep, 2017.)*

It's no surprise then that industry has broadly welcomed the government's announcement – albeit with some caveats about the need for high-level political leadership and NHS commitment to make the project succeed.

Steve Bates, CEO of the BioIndustry Association, said the government's response to AAR was "a key piece in the jigsaw of UK government life science policy that will set the environment for our sector in the lead up to Brexit and beyond. It fits between the publication of the Life Sciences Industrial Strategy in the summer and ahead of both an anticipated Sector Deal and the outcome of the Treasury-led Patient Capital Review later in the year."

The new fast-track pathway should speed up access for NHS patients to the latest therapies "and help to ensure the UK remains a globally attractive cluster in which to start, scale and grow leading life sciences businesses," Bates said.

The fact that Sir Andrew would be chairing the AAC meant "significant industrial insight into the selection process for products able to access this new accelerated route to market," he added.

However, Bates pointed out that "no strategy can succeed without a corresponding plan of action. Polling undertaken by the BIA earlier this year showed that 82% of NHS staff were unaware of either the Accelerated Access Review or the proceeding government strategy Innovation, Health and Wealth."

Moreover, he said, while the government refers to numerous other initiatives such as NHS Test Beds and the Innovation Scorecard, BIA polling "reveals that only 5% of NHS staff are aware of these two programmes. If the Review's ambition for innovation is to truly take hold then it requires both NHS buy-in and top-level government leadership."

The Association of the British Pharmaceutical Industry declared that the move "should benefit thousands of NHS patients as well as delivering significant long-term savings for the health service if appropriate investment in these transformative therapies is made available." Its executive director of commercial policy, Richard Torbett, said it was "incumbent on everyone to tear down the barriers which have prevented access to medical progress of this kind."

On the academic research side, Professor Paul Workman, chief executive of the Institute of Cancer Research, welcomed the new pathway, noting that while the number of treatments and technologies that secured a breakthrough designation "could be quite small," this was "a genuine opportunity" to accelerate access to real innovations.

However, he added, "we also need changes to the way appraisals are made to favour the most innovative drugs ahead of the 'me-toos', and crucially we need action to bring down the sky-high prices of many new medicines."

THE ACCELERATED ACCESS PATHWAY

The core of the initiative is the new accelerated access pathway, which is intended to align and coordinate regulatory, reimbursement, evaluation and NHS diffusion processes for breakthrough innovations. "We will make the process from bench to bedside quicker, cheaper, and easier for innovators and the NHS," the government says.

Its aim is to "bring forward by up to four years patient access to these selected, highly beneficial and affordable innovations." As well as drugs, devices, diagnostics and digital products, these could include "repurposed medicines where a new indication is found for an existing product."

The AAP is designed to complement existing UK initiatives such as the National Institute for Health and Care Excellence's fast-track appraisal process, the NICE/NHS England budget impact test, the Early Access to Medicines Scheme, and the Cancer Drugs Fund. Products will be able to be on the EAMS at the same time as the AAP.

The government expects around five innovations a year to gain breakthrough designation and go onto the new pathway, but stresses the need to avoid any extra costs to the NHS. Any products placed on the AAP "that are cost additive will need to be offset by products

> Aim is to "bring forward by up to four years patient access to selected, highly beneficial and affordable innovations" – UK government

> Commercial engagement will create "a smooth interface for companies throughout the appraisals process"

that deliver cost savings, beyond those already factored into NHS plans," it says. "Efforts will be focused on those products that will deliver the greatest benefit to patients and improve value for money."

Each breakthrough product will benefit from "bespoke case management, which will coordinate across partners to streamline the journey," according to the government. "In return for these commercial benefits, we expect industry to come forward with a cost proposition that delivers additional value for patients and the NHS beyond that achieved under the current system, and is affordable."

To spur collaboration between companies and the NHS when negotiating commercial agreements, the government says that a new strategic commercial unit is to be established in NHS England to give it "enhanced commercial capability" by April 2018. There is "clear demand" from innovators for win-win commercial deals and the new function will be able to develop these types of arrangement.

In parallel, the commercial liaison team at NICE will support commercial engagement between companies and NHS England, "creating a smooth interface for companies throughout the appraisals process."

To speed things up even more, the government also plans to transfer the role of agreeing patient access schemes from the Department of Health to NHS England, which means that from early 2018 companies will need to "begin only one dialogue for each medicine." This, it says, will remove the risk of delays to guidance and "grant earlier certainty for companies about the process of approval."

"TRANSFORMATIVE" DESIGNATION

The government in its response does not go into great detail about the criteria a product will have to meet to merit "transformative" (breakthrough) designation, saying only that "a new transformative designation should be applied to those innovations with the potential for greatest impact."

The AAR itself defined such innovations as "the most strategically important products with the potential to deliver significant benefits in cost or outcomes," and suggested criteria such as significant improvement to patient-relevant outcomes, improved affordability, unmet need, strategic importance to the NHS, alignment with NHS priorities, and clear and measurable outcomes.

HORIZON SCANNING

An important component of the new scheme will be the early identification of what is coming through company pipelines. The new pathway will offer horizon scanning for new technologies to identify a subset of potential breakthrough products that could benefit from the AAP, the government says, adding that this will be a "key capability required for a forward-looking NHS that can articulate its priorities to industry, and prepare to deliver against those priorities."

It notes that the PharmaScan database currently enables horizon scanning for pharmaceutical products, and that NHS England is currently building on these capabilities to create a parallel system suitable for medical technologies. In addition, the recently established National Institute for Health Research Innovation Observatory is now using data analytics to "explore trends in health innovation across drugs, medical technologies, diagnostic tools and healthcare services."

ACCELERATED ACCESS COLLABORATIVE

The job of selecting candidates for the new pathway will fall to the new AAC, which will comprise representatives of the NIHR, NICE, the Medicines and Healthcare products Regulatory Agency (MHRA), NHS England, NHS Improvement and the government.

Input to the AAC will be sought from industry and patient groups that have "sufficient breadth of experience and independence to allow them to inform AAC discussions on the different technology types and conditions those technologies might benefit." Further details will be published on the membership of the AAC, which the government expects to be in place in late 2017.

The government stresses the importance of understanding and evaluating the impact of the new pathway over time. In line with the AAR's recommendation, it says, "we believe that the AAC should be responsible for measuring and evaluating the impact of our accelerated access programme and assessing the industry response to it. The views of the AAC will be informed by parties across the system, who will be represented in the group."

From the editors of Scrip Regulatory Affairs. Published online November 3, 2017

Novartis Seeks EU Accelerated Review For CAR-T Therapy

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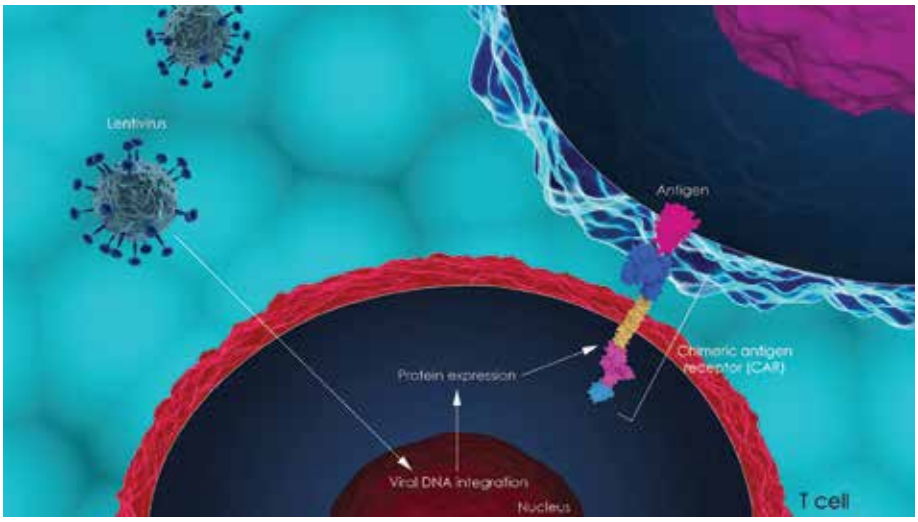

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3d illustration of CAR T-cell therapy

Novartis has applied for approval to market its CAR-T cell therapy CTL019 (tisagenlecleucel) in the EU, and should soon find out whether the European Medicines Agency will agree to fast track its assessment.

The company, which made history in August when CTL019 became the first CAR-T therapy to be approved in the US, this week said it had submitted a marketing authorization application (MAA) to the EMA to market the product as a treatment for leukemia and lymphoma.

Meanwhile, the agency's scientific committee, the CHMP, is to decide over the next few days whether to evaluate the product under the EU's accelerated assessment (AA) procedure. AA can cut the time it takes the CHMP to review a MAA under the centralized procedure from 210 days (not counting clock stops when applicants have to provide additional information) to 150 days. Products granted speedy review must be of major interest for public health or show therapeutic innovation. CTL019 has been granted orphan status in the EU.

"We cannot speculate on the EU assessment procedures or regulatory timelines," a spokesperson for Novartis told the *Pink Sheet* in response to a question about the AA. "We have submitted a robust and comprehensive dossier with our MAA. We expect a CHMP opinion for our application in 2018."

AN IMPORTANT STEP

Novartis appears to be the second company to publicly disclose that it has applied to market a CAR-T therapy in the EU. Its closest rival in the CAR-T space, Kite Pharma, said in July that it had submitted an MAA to the EMA for axicabtagene ciloleucel for treating lymphomas, and that it had been granted accelerated assessment.

Kite, which has since been acquired by Gilead Sciences, has also received US approval for axicabtagene ciloleucel. The product – branded *Yescarta* in the US – was authorized in October, bringing the total number of CAR-T therapies approved by the Food and Drug Administration to two.

Novartis is seeking to market CTL019 in Europe for the treatment of children and young adults with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (ALL) and for adult patients with r/r diffuse large B-cell lymphoma (DLBCL) who are ineligible for autologous stem cell transplant (ASCT).

The approval for the product in the US – where it is called *Kymriah* – covers children and young adults with B-cell ALL that is refractory or has relapsed at least twice. *(Also see "Novartis Beats CAR-T Competitors To The Pricing Punch With Kymriah Approval" - Scrip, 31 Aug, 2017.)* Novartis has since submitted a marketing application to the FDA for the DLBCL indication.

In Europe, Novartis is hoping to build on its US experience with r/r B-cell ALL, and said it was "working closely with [the] EMA and European treatment centers to make CTL019 available in this region."

According to Datamonitor Healthcare analyst Ali Al-Bazergan, the EU submission is "an important step to the company's goal in leveraging Kymriah to provide a comprehensive solution to B-cell cancers. By opening its market to Europe and to DLBCL, Novartis will be well entrenched to achieve its touted blockbuster sales."

As for the company's efforts outside Europe and the US, the Novartis spokesperson said there were plans for "additional regulatory submissions for CTL019 in pediatric and young adult patients with r/r B-cell ALL and adult patients with r/r DLBCL in Canada, Australia, Switzerland and Japan in 2018. Additional markets are being evaluated in order to provide greater patient access to CTL019."

EMA'S PRIME

Notably, CTL019 and axicabtagene ciloleucel in Europe had both been granted access to PRIME, the EMA's popular priority medicines scheme for getting drugs for unmet medical needs to patients faster. Drug developers accepted on the scheme are offered early and proactive support from the EMA to help optimize their development plan, and the opportunity of having their eventual MAA reviewed under the AA procedure. Of the 31 products to have been accepted on the scheme since its launch in March last year, Novartis and Kite appear to be the first companies to have publicly disclosed they had reached the MAA stage.

THE EU SUBMISSION

Novartis's EU MAA is based on Phase II results from the company's global, multi-

center, ELIANA and JULIET trials.

ELIANA, which assessed CTL019 in patients with ALL, is "the first pediatric global CAR-T cell therapy registration trial, examining patients in 25 centers in the US, Canada, Australia, Japan and the EU," Novartis said. The Phase II results had been used to support US approval for the ALL indication.

JULIET is the first multicenter global registration study for CTL019 in adult patients with r/r DLBCL. It is also the largest study examining a CAR-T therapy exclusively in DLBCL, Novartis said, adding that the trial is enrolling patients from 27 sites in 10 countries across the US, Canada, Australia, Japan and Europe. Phase II JULIET study results have been used to support Novartis's US submission for the DLBCL indication.

Data from the six-month primary analysis of JULIET are to be presented at the annual meeting of the American Society of Hematology (ASH) in December 2017, the company noted.

CTL019 is manufactured for each individual patient using their own cells at Novartis's Morris Plains, New Jersey facility. Novartis said it had designed "a reliable and integrated manufacturing and supply chain platform that allows for an individualized treatment approach on a global scale." Having manufactured CAR-T cells for more than 250 patients from 11 countries across various indications in clinical trials, Novartis said it had demonstrated a reproducible product.

> "JULIET is the first multicenter global registration study for CTL019 in adult patients with r/r DLBCL. It is also the largest study examining a CAR-T therapy exclusively in DLBCL, Novartis said.

The company also noted that it had established the CTL019 manufacturing process at the Fraunhofer-Institut for cell therapy and immunology (Fraunhofer-Institut für Zelltherapie and Immunologie) facility in Leipzig, Germany, which currently supports the manufacturing of CTL019 for global clinical trials.

PATISIRAN ALSO SEEKING AA

CTL019 is one of two products that the CHMP is assessing with regard to granting an AA at its monthly meeting this week. The other is Alnylam Pharmaceutical's orphan drug patisiran for treating polyneuropathy in patients with ATTR amyloidosis. Patisiran, an investigational RNAi therapeutic, met its primary efficacy endpoint and all secondary endpoints in the Phase III APOLLO study, the company said in September. *(Also see "APOLLO Success Clears Alnylam For Lift-Off" - Scrip, 20 Sep, 2017.)* Alnylam formed an alliance with Sanofi Genzyme in 2014 to accelerate the advancement of RNAi therapeutics as a potential new class of innovative medicines for patients with rare genetic diseases.

From the editors of Scrip Regulatory Affairs. Published online November 7, 2017

Biosimilar Coding Policy For Medicare Reversed To 'Promote Innovation'

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The US Centers for Medicare and Medicaid Services (CMS) has agreed to change its approach to reimbursing biosimilars under Medicare Part B in a way that will promote more innovation and competition, the agency says in a final rule released Nov. 2.

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Beginning Jan. 1, 2018, all biosimilars will be reimbursed using unique Medicare payment codes, known as Healthcare Common Procedure Coding System (HCPCS) codes, based on individual prices. The approach has been strongly supported by biosimilar developers. *(Also see "Medicare Coding Change For Biosimilars Could Save $65bn, Firms Say" - Pink Sheet, 14 Sep, 2017.)* CMS' decision was published as part of the 2018 Medicare physician fee schedule final rule.

CMS had previously announced it would reimburse biosimilars referencing the same innovator drug under the same code and at a single blended price. CMS announced in July it was considering reversing that policy in the proposed version of the physician payment rule and requested public comments on the change. *(Also see "Biosimilars Payments In Medicare: CMS Signals Willingness To Change" - Pink Sheet, 17 Jul, 2017.)*

The earlier policy, released in January 2016, reflected the Obama Administration's concern with keeping biosimilar prices in check. CMS' decision to reverse it reflects the current Administration's willingness to re-evaluate past approaches in a way that addresses industry's concerns.

'WE ARE PERSUADED'

"We seek to promote innovation, to provide more options to patients and physicians, and to encourage competition to drive prices down," CMS says in the new rule.

"Based on the review of the comments … we are persuaded that changing the Part B biosimilar payment policy to provide for the separate coding and payment for products approved under each individual abbreviated application, rather than grouping all biosimilars with a common reference product into codes, will meet this stated goal."

There is no change to the requirements that Part B payments for biosimilars will be based on their average sales price (ASP) plus 6% of the ASP of the reference drug or that reference drugs are reimbursed separately under their own codes.

The decision to reverse the policy was applauded by the Biosimilars Forum, a group representing biosimilar developers. "The Biosimilars Forum is delighted to learn of CMS' decision, which is a huge win for patients," said President Stacie Phan.

"It's clear that CMS valued the additional thought and analysis provided by the countless number of stakeholders who expressed concern that the long-term stability of the biosimilar market would be jeopardized unless they reconsidered its policy."

GUIDANCE ON CODING DETAILS COMING

The agency will issue "detailed" guidance on coding in the coming months, including instructions for new codes for biosimilars that are currently grouped into a common payment code, and on the use of modifiers, CMS says.

Of the three biosimilars currently on the market in the US, two that reference **Johnson & Johnson**'s *Remicade*– **Merck & Co. Inc.**'s *Renflexis* (infliximab-abda) and **Pfizer Inc.**'s *Inflectra* (infliximab-dyyb) – currently share a code and would be impacted by the change in policy. *(Also see "What Renflexis Pricing Says About Medicare's Biosimilars Policy" - Pink Sheet, 27 Jul, 2017.)*

CMS' previous coding policy involved the use of modifiers in addition to the suffixes required by FDA to help distinguish biosimilars in claims data for safety monitoring.

The process of revising biosimilar coding systems is expected to take about six months. "Completion of these changes, which will require changes to the claims processing systems, is planned to occur as soon as feasible, but should not be expected to be completed by Jan. 1, 2018," the agency cautions.

"We anticipate that this will be done by mid-2018 and we plan to issue instructions using sub-regulatory means, such as change requests/transmittals to contractors and the ASP website."

In an analysis comparing the use of separate and single codes for biosimilars, CMS predicts that separate codes will lead to greater uptake of biosimilars, more biosimilars on the market, and decreasing (or at least stable) reference product prices after 10 years.

However, the agency notes there is little data so far on the biosimilars market and it may undertake further analysis in this area as the market develops. Issues that could be addressed in the future include:

- Whether small molecule drug pricing, utilization and models apply to biosimilars;
- To what extent experience with nationwide reference pricing, such as in Europe, informs Medicare pricing policy; and
- The key parameters for determining the "optimal tradeoff between short-run price savings and long-run incentives to innovate."

Published online November 3, 2017

US FDA TO SPONSORS: No Dice On Appealing Advice Through Dispute Resolution

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Drug and biologic product sponsors may request higher level review of US FDA advice on development programs, just not through the agency's formal dispute resolution process.

In a final guidance announced in the Federal Register Nov. 6, FDA stands by its view, staked out in a September 2105 draft guidance, that advice conveyed to sponsors in meeting minutes or correspondence is not an appropriate subject for a formal dispute resolution request.

That position had drawn objections from pharmaceutical industry representatives, who argued in comments on the draft guidance that FDA was inappropriately narrowing the scope of issues that could be appealed through dispute resolution.

Although the agency was unswayed, the final guidance explains that sponsors may approach a higher management level to further discuss agency advice in meetings established under the prescription and generic drug and biosimilar user fee programs.

FDA's final guidance also makes clear that the formal dispute resolution process is intended for drug and biologic product sponsors and not for nonsponsors.

Sponsors may approach a higher management level to further discuss agency advice in meetings established under the prescription and generic drug and biosimilar user fee programs.

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COMPLETE RESPONSE LETTERS STILL APPEALABLE ...

The final guidance, "Formal Dispute Resolution: Sponsor Appeals Above the Division Level," explains procedures for resolving scientific and medical disputes between sponsors and the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) that cannot be resolved at the division level.

Historically, few dispute resolution appeals are granted in full, although sponsors often get clarity on a path forward. *(Also see "If At First You Don't Succeed, Try Dispute Resolution" - Pink Sheet, 9 Dec, 2013.)*

In rare cases, a dispute resolution request may lead to an advisory committee meeting or a sponsor's preferred outcome. *(Also see "FDA Reverses Position On Fabre-Kramer's Gepirone, Clearing Way For Approval" - Pink Sheet, 17 Mar, 2016.)*

Some companies have used the formal dispute resolution pathway multiple times for the same product. **PTC Therapeutics Inc.** twice appealed refusal-to-file letters for its muscular dystrophy drug *Translarna* (ataluren). Both appeals were denied, and the new drug application eventually was filed under protest. *(Also see "Exondys Revisited? Translarna Brings Efficacy Woes Into US Panel Review" - Pink Sheet, 26 Sep, 2017.)*

Following a negative advisory committee review of the ataluren NDA, FDA issued a complete response letter in October, requesting additional clinical data to demonstrate substantial evidence of efficacy. *(Also see "PTC To Appeal Translarna's Complete Response Letter From US FDA " - Pink Sheet, 25 Oct, 2017.)* During PTC's Nov. 2 earnings call, CEO Stuart Peltz said the company expected to file a formal dispute resolution letter and looked forward "to interacting with the Office of New Drugs during the course of this appeal."

Complete response letters are one of several regulatory actions identified in the final guidance as appropriate for formal dispute resolution. Others include: an investigational new drug application (IND) clinical hold; denial of a breakthrough therapy designation request; denial of a proprietary name review request; and refuse-to-receive letter for an abbreviated new drug application (ANDA).

... BUT DEVELOPMENT PROGRAM ADVICE IS NOT

As in the draft guidance, the final document explains that agency communications such as meeting minutes or general advice letters typically include recommendations or advice to a sponsor that generally convey CDER's or CBER's current thinking on a particular topic and are not appropriate for formal dispute resolution. *(Also see "Dispute Resolution Strategies: FDA Clarifies Which Issues Can Be Appealed" - Pink Sheet, 21 Sep, 2015.)*

"Sponsors are not bound by such recommendations and/or advice," the final guidance states. "Sponsors can follow the advice in meeting minutes or other correspondences, or they can use an alternative approach, if the approach satisfies the requirements of the applicable statutes and regulations."

The Pharmaceutical Research and Manufacturers of America (PhRMA) and the law firm Hyman Phelps and McNamara had

both objected that by eliminating the ability to appeal agency advice on drug development programs, the draft guidance significantly narrowed the scope of disagreements that can be appealed through the formal dispute resolution pathway.

"FDA often communicates decisions of great significance to sponsors – particularly essential study design decisions – in these letters, even if they are not officially binding," PhRMA's December 2015 comments on the draft guidance state.

"Excluding these disputes from the FDR process significantly narrows its scope in a manner that is likely to harm sponsors' ability to gain certainty and a fair hearing during drug development – especially when a particular division may be adamant about its position on a key study design issue," PhRMA said. "Without an appeal right, these sponsors will face the choice of proceeding with a study design 'at risk' or conducting the study the division has demanded, which may be unnecessarily more burdensome."

PhRMA also asserted the draft guidance was inconsistent with the Prescription Drug User Fee Act V (PDUFA V) commitment letter provisions on dispute resolution. The commitment letter includes "no limitation on the manner in which a dispute must arise for the PDUFA goals to apply – and certainly no restriction to regulatory actions having scientific and/or medical significance, nor situations where sponsors are bound by FDA's stated position," PhRMA said.

Hyman Phelps and McNamara said disallowing use of the formal dispute resolution process for agency advice communicated in meetings and letters would mark a "substantive change" in practice.

Although the outcome of an End-of-Phase II meeting may not be a "regulatory action" as that phrase was used in the draft guidance, "it is an agreement – or lack of agreement – on an important topic that may significantly affect development of the product at issue," Hyman Phelps' comments state.

"An inability to appeal through the FDR process leaves sponsors with the untenable choice set forth in the 2015 draft guidance: follow the advice in the meeting minutes or use an alternative approach 'if the approach satisfies the requirements of the applicable statutes and regulations,'" Hyman Phelps said, noting that the "key question" is whether the sponsor's alternative approach will meet the legal requirements.

> "Except in unusual circumstances, CDER and CBER generally do not intend to accept requests by nonsponsors for internal agency review of a scientific and/or medical issue regarding an application or submission."
> – FDA

MEETING OPPORTUNITIES UNDER USER FEE PROGRAMS

Despite the objections raised in public comments, the final guidance reiterates that advice communicated in meeting minutes and other correspondence is not a regulatory action taken by CDER or CBER and, therefore, is inappropriate for formal dispute resolution.

However, the final document explains that sponsors may approach the review division or the next highest management level to further discuss advice provided in meeting minutes or other correspondences related to a clinical development program outside of a formal dispute resolution request.

The forum for such interactions should be meeting opportunities provided under PDUFA, the Biosimilar User Fee Act (BsUFA) and the Generic Drug User Fee Act (GDUFA).

"For example, sponsors may request a Type C guidance meeting under PDUFA, a biosimilar biological product development (BPD) Type 2 meeting under BsUFA, or a meeting under GDUFA with the review division, and request the next highest management level be present at the meeting (typically in a nondecisional capacity)," the guidance states.

FDA's tweaking of the final guidance seems unlikely to satisfy those who objected to the draft guidance provisions.

"In short, I didn't see the finalized guidance as making any real changes," said Josephine Torrente, a director at Hyman Phelps who submitted the firm's comments on the draft guidance.

DISPUTE RESOLUTION RESERVED FOR PRODUCT SPONSORS

In the final guidance, FDA clarifies that the formal dispute resolution procedures are only for sponsors and do not apply to other individuals or entities that wish to appeal a scientific or medical issue regarding an application regulated by CDER or CBER.

"Except in unusual circumstances, CDER and CBER generally do not intend to accept requests by nonsponsors for internal agency review of a scientific and/or medical issue regarding an application or submission," the agency states in a footnote.

"The agency believes that it is highly unlikely that an individual or entity other than the sponsor would have access to the information necessary to support a request for internal agency review of these types of decisions," the guidance states. "The agency also believes that it is highly unlikely that a nonsponsor would be in a position to evaluate any product development considerations that may be affected by an agency decision for which a nonsponsor might wish to request internal agency review."

The final guidance also was updated to reflect the GDUFA II timelines for reviewing disputes involving ANDAs.

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FDA Adds 'Doctor' To CV Statement For OTC Aspirin Labeled With Hearts

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OTC aspirin makers often use cardiovascular imagery on packages to attract consumers interested in using the products to help reduce chances of a heart attack or stroke. FDA now is instructing US marketers to include information more pointedly suggesting that these consumers consider first seeking physician advice,

In final guidanceannounced Nov. 6, FDA makes clear that it not only expects OTC aspirin marketers to include a statement referring to doctors when package labels include a heart or other image suggesting a CV indication, but also that they bear this specific statement: "Talk to your doctor or other healthcare provider before using this product for your heart." A draft issued nine months earlier proposed a similar but shorter and more general recommended statement, using "Consult your healthcare provider …" rather than "Talk to you doctor or other healthcare provider …" *(Also see "Aspirin Wearing Hearts On Packages Needs CV Statement, Too – CDER" - Pink Sheet, 12 Jan, 2017.)*

Issued by FDA's Center for Drug Evaluation and Research, the policy applies to aspirin-containing OTCs with CV-related imagery marketed under the tentative final monograph for internal analgesic, antipyretic and antirheumatic OTC drugs. It does not set a specific date or period of time for compliance with the policy.

In response to the new final guidance, **Bayer AG** said it is considering how it will change labeling currently used for most *Bayer Aspirin* products that includes a statement similar but not identical to FDA's recommended language.

A spokesman for Bayer's US consumer products business said most Bayer Aspirin formulations labeled with CV imagery already include the statement, "aspirin is not appropriate for everyone, so be sure to talk to your doctor before you begin an aspirin regimen."

The firm "is currently reviewing the FDA guidance and will consider how to incorporate FDA's new recommended statement into its aspirin labeling," the spokesman said.

Other firms subject to the guidance also face adding the 15-word statement in a manner that satisfies FDA, a potential challenge given limited space on package fronts and other multiple information items required there.

The guidance says the recommended statement should appear in reasonable proximity to the CV-related imagery and with similar prominence in at least 6-point type size font on the principal display panel. It also states that it does not address alternative language, other health imagery or other CV claims on consumer-directed label or labeling that "may otherwise misbrand the product."

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Firms subject to the guidance face adding the 15- word statement in a manner that satisfies FDA, a potential challenge given limited space on package fronts and multiple information items required there.

Potential side effects from long-term aspirin therapy prompted the agency to recommend that any CV-related imagery on OTC aspirin labels be paired with a statement that reminds consumers to talk to doctors or other health care providers before using aspirin for the professional indication of secondary prevention of cardiovascular diseases, the guidance says.

"More specifically, FDA does not intend to take action against manufacturers of single-ingredient aspirin, buffered aspirin, and aspirin in combination with an antacid, marketed pursuant to the TFM for IAAA Drug Products because the product label includes cardiovascular-related imagery such as the heart image, if the label also includes the" statement printed in the guidance, CDER says.

In addition to hearts, CV-related imagery displayed on some OTC aspirin principal display panels include electrocardiography graphics and stethoscopes around heart images. Aspirin's indication for the secondary prevention of CV events, such as recurrent heart attack or ischemic stroke, is approved only under the direction of a physician.

OTC aspirin products that do not include cardiovascular-related imagery on PDPs are not subject to the guidance.

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

LOST IN TRANSLATION: Rx Drug Used Where OTC Hydrocortisone Belongs

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A manufacturer in China incorrectly translated ingredient names and "always" has used the Rx corticosteroid dexamethasone in a drug distributed in the US as an OTC hydrocortisone topical, according to FDA.

The product made by Zhanjiang Jimin Pharmaceutical Co. Ltd., of Guangdong, China, was distributed in the US by Lucky Mart Inc. under the brand *Piyanping Anti-Itch Lotion* and has been on recall since Aug. 30. FDA assigned its most urgent recall classification, for products that pose reasonable probability of serious adverse health consequences or death, to the Piyanping Anti-Itch recall, the agency's recall database indicates.

In a warning letter published Nov. 7, the Office of Manufacturing Quality in the Office of Compliance of FDA's Center for Drug Evaluation and Research said during a May inspection of Zhanjiang Jimin Pharmaceutical's plant, investigators questioned the firm about a discrepancy between labeled active ingredients and finished product testing records for the hydrocortisone-labeled product.

"They were told that there was a translation mistake where firm management had thought hydrocortisone was the same material as dexamethasone. Your firm further explained that they had always purchased dexamethasone acetate for use in Piyanping Anti-Itch Lotion and had never purchased hydrocortisone API," the letter states.

However, dexamethasone is not included in any OTC drug monograph for any indication, including external analgesic antipruritic uses, and FDA is not aware of evidence a product with the same formulation as Piyanping Anti-Itch Lotion is otherwise eligible for inclusion in ongoing monograph rulemakings.

Zhanjiang Jimin Pharmaceutical received from FDA a National Drug Code number needed to market the product in April 2011. Piyanping Anti-Itch labeling includes Mandarin language characters as well as English text, indicating the product is targeted for an immigrant community.

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FDA advised the company that using dexamethasone as the active pharmaceutical ingredient rather than hydrocortisone is an indication of good manufacturing practices problems.

According to FDA's Orange Book, dexamethasone-containing Rx ointments are ophthalmic treatments, used for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial ocular infection exists. The ingredient also is available Rx in oral delivery formats.

In its announcement of the recall following FDA's inspection of Zhanjiang Jimin Pharmaceutical, Lucky Mart said multiple-daily uses of a dexamethasone-containing topical could cause serious side effects including whitening or thinning skin; adrenal suppression such as high blood sugar, weakened immunity, electrolyte imbalances, emotional lability and slowing of growth in children; and glaucoma and cataracts. The South El Monte, Calif., firm said it had not received any reports of adverse events related to the product.

GMPS AT CORE OF PROBLEM

FDA advised Zhanjiang Jimin Pharmaceutical that using dexamethasone as the active pharmaceutical ingredient rather than hydrocortisone is an indication of good manufacturing practices problems. The error showed the firm did not have adequate quality control unit for approving or rejecting ingredients and all other components that make up a drug product manufacturing process, CDER's OMQ said in the letter submitted Oct. 30.

Additionally, although Zhanjiang Jimin Pharmaceutical recalled all lots of the noncompliant drug product distributed to the US, FDA is not confident the mistake will not recur.

"You have not provided details of an investigation of the failure of your quality unit and your action plan to prevent recurrence. You also have not provided details of an evaluation to ensure all the drug products you released for distribution to the US were manufactured with appropriate components," the letter states.

Another GMP problem at Zhanjiang Jimin Pharmaceutical was the absence of appropriate laboratory determination of satisfactory conformance to final specifications for a drug product, for each batch. "Testing your active ingredients is essential to ensuring the drug products you manufacture meet their established specifications for chemical attributes they purport to possess," FDA advises the firm.

Additionally, Zhanjiang Jimin Pharmaceutical was noncompliant with the drug

GMP requirement to establish adequate written procedures for production and process control designed to assure that the drug products its manufactures have the identity, strength, quality and purity they purport or are represented to possess

FDA recommended Zhanjiang Jimin Pharmaceutical retain a regulatory consultant to guide its remediation into GMP compliance. In addition to providing insufficient information on its recall procedures, the firm's Aug. 16 response to FDA's findings did not convince the agency that it has:

- quality control test methods and specifications to analyze each drug batch prior to a batch release decision, including chemical and microbial quality attributes;
- "a clear commitment" to testing products for identity and strength of active ingredients and all other appropriate quality attributes, including total count and objectionable microorganisms;
- specific timelines for process performance qualification for each products and a detailed summary of its approach for routinely monitoring intra-batch and inter-batch variations.

Piyanping Anti-Itch Lotion also was misbranded because with the API dexamethasone, it is not indicated for its labeled use, "Temporarily relieves itching associated with minor skin irritations, inflammation, & rashes."

OTC drugs intended for the relief of itching and other external analgesic uses are available under a tentative final monograph as FDA evaluates their classification as generally recognized as safe and effective.

The FDA warning to Zhanjiang Jimin Pharmaceutical is one of a spate of drug GMP warning letters to foreign manufacturers in recent months, particularly to firms in Asia. Of FDA's 110 drug GMP warning letters in 2016, 29 went to firms in Asia, most of them in China and India. *(Also see "FDA Hits Two More Asian Firms With Drug GMP Warning Letters" - Pink Sheet, 20 Sep, 2017.)*

From the editors of the Tan Sheet.
Published online November 8, 2017

'Not Enough Time' To Transfer All Marketing Authorizations In Case Of 'No-Deal' Brexit, says EFPIA

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Almost half of the member companies of the European pharmaceutical industry federation, EFPIA, expect delays to trade in medicines if the UK leaves the EU without a deal and falls back on World Trade Organization rules.

In such an event there would not be enough time in the period to the March 2019 Brexit date to transfer up to 12,000 European marketing authorizations held in the UK, and thousands of review months would be required to move batch release activities out of the UK. Moreover, half of the 1,500 clinical trials underway in the EU with a UK-based sponsor will still be ongoing by the Brexit date.

These are just a few of the alarming statistics to emerge from a survey conducted by EFPIA among its members. Concerns about trade, marketing authorizations, and other regulatory implications of Brexit have already been widely aired *(Also see "Massive Reallocation of UK Rapporteurships Likely As EMA Plans For Future; UK's Interim Role Uncertain" - Pink Sheet, 11 May, 2017.)* but the survey results serve to put some flesh on the bones.

The survey's results underline "the sheer scale and importance of the medicines issues that must be addressed as part of the Brexit discussions in order to protect public health," EFPIA said.

Stressing the need for urgent action on some form of regulatory collaboration agreement post-Brexit, the federation's director general, Nathalie Moll, said the UK and the EU "cannot afford to wait any longer to ensure that the necessary cooperation on medicines is in place from the day the UK leaves the EU."

To illustrate some of the challenges facing the industry in the event of a "no-deal" Brexit, EFPIA noted that more than 2,600 finished medicinal products sold across the EU have some part of their manufacturing process conducted in the UK. Around 45 million product packs are supplied from the UK to the other 27 EU and EEA (European Economic Area) member states each month, and more than 37 million packs travel in the opposite direction.

"In this context, 45% of EFPIA members expect trade delays if the UK and

> Survey underlines "the sheer scale and importance of the medicines issues that must be addressed as part of the Brexit discussions" – EFPIA

Europe fell back to WTO rules," EFPIA said. To prevent these delays, the EU and UK "should agree a comprehensive agreement that ensures maximum alignment between EU and UK pharmaceutical laws."

It noted that 400 centrally authorized products have a UK legal entity as the marketing authorization (MA) holder, and given that there are multiple MAs per product, a total of 2,400 MAs will need transferring to a legal entity in the EU if they are to continue being marketed. EFPIA estimates that these transfers will take up a total of 5,000 review months based on a standard 60-day transfer timeline.

There will also be problems for products approved through the decentralized and mutual recognition systems in Europe: 5,800 MAs held by UK legal entities will need to be transferred.

There is not enough time between now and March 2019 to transfer all these marketing authorizations and "a more flexible approach is needed from regulators," EFPIA said.

BATCH RELEASE AND CLINICAL TRIALS

Another area where additional costs and disruption are inevitable in the event of a no-deal Brexit is the need to move batch release activities out of the UK. At present, according to EFPIA, 60% of its members conduct batch release from the UK, amounting to a total of 1,300 products sent out for EU distribution from UK sites.

Moving these sites would involve some 4,000 review months based on a 90-day standard Type II CMC (chemistry, manufacturing and controls) variation timeline, EFPIA said. It also noted that 40% of its member companies believe that their qualified person and laboratory capacity is insufficient for the retesting of products released from the UK, raising the specter of shortages and supply disruptions.

On the clinical trials front, a total of 1,500 studies are currently under way in multiple EU countries with the UK as sponsor, and half of those will still be ongoing in March 2019, the survey found. The figures "underline the importance of scientific research collaboration between the UK and EU. Scientific collaboration strengthens the EU's global position in life sciences, attracting global life science investment to the EU," EFPIA commented.

"Even in the context of the Brexit negotiations where all sectors are looking for clarity on the future, it is important to recognise that the medicines sector is different," Moll stated. "The medicines we make impact directly on peoples' health. Securing ongoing cooperation on medicines regulation between the UK and EU is the best way of ensuring that patients across Europe continue to have access to safe and effective medicines."

From the editors of Scrip Regulatory Affairs. Published online November 7, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Clinical development plan for Pfizer's Staphylococcus aureus vaccine intended for pre-surgical prophylaxis in elective orthopedic surgical populations	Vaccines and Related Biological Products	Nov. 7
Bayer HealthCare Pharmaceuticals' ciprofloxacin inhalation powder for reduction of exacerbations in non-cystic fibrosis bronchiectasis adult patients (>18 years of age) with respiratory bacterial pathogens	Antimicrobial Drugs	Nov. 16
Bulk drug substances nominated for inclusion on the Sec. 503A Bulks List and drug products nominated for inclusion on the list of drug products that present demonstrable difficulties for compounding under Sec. 503A and 503B ("Difficult to Compound List")	Pharmacy Compounding	Nov. 20-21
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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Phil Jarvis, Mike Ward

CORPORATE SALES
John Lucas, Elissa Langer

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Christopher Keeling

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Jean Marie Smith

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Denise Peterson
Nielsen Hobbs
Mary Jo Laffler

Europe
Eleanor Malone
Maureen Kenny
Alex Shimmings

Asia
Ian Haydock

POLICY AND REGULATORY

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Eileen Francis
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