REGULATORY UPDATE
Woodcock Wants Rapid Regulatory Policy Development, p. 9

NEW PRODUCTS
Biomarker-Led Claim Is Small Step For Merck's Keytruda, Giant Leap For Cancer Indications, p. 7

CONSUMER DRUGS
Two-Tier OTC Monograph Approach Could Come With User Fee Revamp, p. 16

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EMA's PRIME A Year On: Hits And Misses When It Comes To Applications

NEENA BRIZMOHUN neena.brizmohun@informa.com

Weak pharmacological rationale. Issues with the robustness of data including the use of comparisons to inadequate historical control data. Failure to justify a therapeutic advantage.

These are some of main reasons almost three out of four applications have been denied entry on the European Medicines Agency's priority medicines (PRIME) scheme for drugs for unmet medical need.

Very few applications, though, have been rejected because of a failure to justify PRIME's eligibility criterion of unmet medical need, according to Robert Hemmings, a senior official at the UK regulator, the MHRA, and chair of the EMA's scientific advice working party.

> The nine applications the EMA receives on average per month for PRIME is in line with expectations.

Hemmings was speaking on May 19 at a meeting the EMA hosted at its headquarters in London to mark the first anniversary of PRIME and experience with the scheme since it was launched in March 2016. He provided valuable insight into what the EMA expects of drug developers who want to apply for the popular scheme that offers them enhanced scientific and regulatory support from the agency, and the chance of having their product reviewed under the EU's accelerated assessment procedure.

As of April 21, the EMA had received 108 requests for entry into PRIME. It had processed 96 requests, granted PRIME designation to 20, and rejected 71; the remaining five applications were deemed to be out of scope of the scheme. An additional five investigational drugs were accepted on the scheme last week, but these were not included in the data Hemmings presented at the meeting. *(Also see "Accelerated Assessment Decision 'Imminent' For Two Products In EMA's PRIME Scheme" - Pink Sheet, 19 May, 2017.)*

The agency received nine applications on average per month, which is "about in line with expectations," Hemmings said, noting that the agency had originally predicted it would get around 10 applications per month. The quality of the applications received is "generally high," he added.

CONTINUED ON PAGE 4

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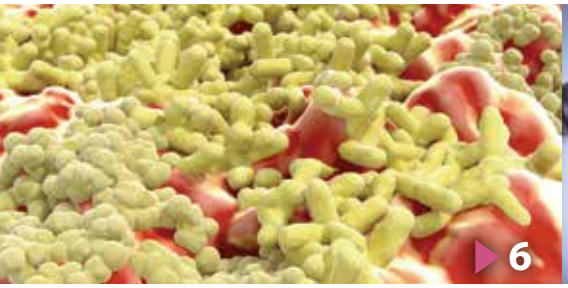
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HHS Action On Drug Pricing: Here's Who Secretary Price Is Listening To

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HHS is expected to move ahead with action to address high drug prices following a series of stakeholder roundtables held over the past month.

J&J Settlement With States Not Likely To Be Precedent In OTC Space

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J&J's agreement with 42 states and Washington, D.C. is its latest cost from widespread GMP problems that prompted recalls and led to a 2011 FDA consent decree. But the unusual combination of factors suggest more such state actions are unlikely to follow.

FDA, EU To Redouble Inspection Of Asian Pharmaceutical Supply Chains

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Mutual recognition agreement enables US and European authorities to redirect inspectional resources to China and India. The result could be more warning letters and other actions unless global companies strengthen oversight of ingredient suppliers and contract manufacturers in Asia, current and former FDA officials say.

European CHMP Recommendations & MAA Updates

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Recommendations on drugs awaiting approval from the European Medicines Agency's Committee for Medicinal Products for Human Use, and updates on the marketing authorization applications for individual products.

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CONTINUED FROM COVER

The vast majority of requests for PRIME designation were for the therapeutic area of oncology (31 applications were submitted, of which 6 were granted designation). This is "perhaps not surprising," Hemmings said. The unmet medical need in a number of oncology settings "is rather easy to justify." Also, there is a lot of industry development going on in the area of oncology.

The other therapeutic areas for which products have received a PRIME designation are hematology-hemostaseology (11 applications, of which 6 were granted); neurology (8 applications, 2 granted); gastroenterology-hepatology (5 applications, 2 granted); vaccines (4 applications, 1 granted); immunology-rheumatology-transplantation (4 applications, 1 granted); endocrinology-gynecology-fertility-metabolism (3 applications, 1 granted), and psychiatry (1 application).

Therapeutic areas for which applications failed to make the grade are: infectious diseases (7 applications); cardiovascular diseases (6); pneumology-allergology (4); ophthalmology (3); dermatology (2); diagnostic (1); and musculoskeletal system (1).

As for substance type, 32 applications where for a chemical drug (5 granted); 31 were for an advanced tissue medicinal product or ATMP (12 granted); 17 were for a biological (2 granted); and 11 came under the category of "other," of which 1 was granted for a vaccine.

MOST APPLICATIONS AT 2ND ENTRY POINT

There are two entry points for PRIME eligibility applications. The proof-of-principle entry point is for SMEs and academics only who are likely to need more help from the agency and, as such, they can apply at an earlier stage of development when they have compelling non-clinical data and tolerability data from initial clinical trials. The proof-of-concept entry level is for any type of sponsor who has preliminary clinical evidence in patients to demonstrate the promising activity of the medicinal product and its potential to significantly address an unmet medical need.

A total of 86 applications were submitted at the proof-of-concept entry level. Of the 5 that were filed at the proof-of-principle level, only 1 was accepted onto the scheme, Hemmings said.

> "Eighty-six applications were submitted at the proof-of-concept entry level but just five at the proof-of-principle level.

The vast majority of applicants seeking entry via the proof-of-concept level have been at the Phase II or Phase I-II stage of clinical development. A total of 39 applications were based on Phase II data, 24 were based on Phase I-II data, and 18 were based on only Phase I data.

Regarding PRIME-designated products, study data from randomized and controlled trials, and how many patients are involved in a study, the EMA found there was "no correlation between the study type, number of patients and success rates".

Some applications via the proof-of-concept entry level were rejected because the product was already in the late stage of development. Hemmings reiterated that the main focus of PRIME is to support applicants who are at an early stage of their drug development. Applications during the late stage of development have been "a blocking issue" for some products, he said, even if both the unmet medical need and proof-of-concept boxes are ticked. "If the product is for an area that "we know well [and] we've perhaps got some regulatory experience in assessing in that area [and] we've seen products go through the rest of the system – the HTAs [health technology assessments] and payers, etc – then there's little additional regulatory and scientific support that we can give at this stage."

NOTABLE EXCEPTIONS

On the other hand, the EMA assessed 2 applications based on Phase III data. These are "notable exceptions," Hemmings said, explaining that the EMA was willing to use PRIME for later stage development where "the value of the scientific and regulatory support is still worth giving."

Such cases are where the "type of intervention is so novel or the therapeutic setting is different from what we've experienced before, and different from what the healthcare system has had to deal with before." In addition, the PRIME scheme could be useful where such applicants might be seeking an accelerated assessment and need scientific and regulatory support regarding post-authorization issues such as when it comes to preparing their risk management plan. "The more you can work on those aspects of the post-authorization in these settings, you're still adding value from the PRIME scheme."

FAILURE TO PROVIDE ROBUST DATA

As for other reasons for proof-of-concept level applications being rejected, a large number of denials were because of issues with the robustness of the data submitted and "whether the data we have available is sufficiently reliable to substantiate the proof-of-concept," according to Hemmings. Examples of concerns relating to data robustness are:

- trial design issues, for instance, where the treatment effect is not isolated from other factors, use of concomitant treatments;
- inconsistency of results across studies, study groups or endpoints;
- the claim in the subgroup has not been sufficiently justified;
- sample issues relating to size, heterogeneity, insufficient information on baseline; and
- comparison to inadequate historical control data.

A number of denials for PRIME designation were because of a failure to show a sufficient effect size. As such, the application did not meet PRIME's criteria that require products to bring a major thera-

peutic advantage if an existing treatment exists or demonstrate a major impact on public health.

USING LITERATURE AND EXTRAPOLATING DATA

Another issue the EMA has deliberated over concerns the acceptance of PRIME applications based on literature. Such applications are more acceptable at the proof-of-principle entry level, according to Hemmings' slide presentation. In addition, reliable, trustworthy and high quality literature would need to be used. Also, the use of literature may not be applicable similarly between chemicals, biologicals and ATMPs.

As for using data extrapolated from other products, Hemmings' slide presentation said the EMA had discussed the need for data to be generated with the product itself, while acknowledging "the possibility for other products' data to be supportive (eg, in cases with surrogate marker validated)."

PROOF- OF-PRINCIPLE REJECTS

The main reasons the EMA rejected four of the five applications that were submitted at the proof-of-principle entry level were:

- weak pharmacological rationale, insufficient nonclinical evidence on the claimed mechanism of action;
- limited relevance of animal models presented; and
- insufficient pharmacokinetic exposure data to support expected clinical outcome.

A PERFECT WORLD

In conclusion, Hemmings outlined what the EMA expected from applicants when it comes to granting eligibility to PRIME. Applicants need to target an unmet medical need, ie there must and no existing treatments, or if there are, they must demonstrate clear limitations of existing therapies.

They should provide nonclinical data supporting the pharmacological rationale. There should be clinical exploratory data on relevant endpoints. If uncontrolled, comparable historical control should be used, ie there is a need for sufficient information on baseline characteristics. And the magnitude of the effect size should support major therapeutic advantage.

From the editors of Scrip Regulatory Affairs. Published online May 24, 2017

Getting On – And Staying In – the EMA's PRIME Scheme

NEENA BRIZMOHUN neena.brizmohun@informa.com
MAUREEN KENNY maureen.kenny@informa.com

Products on the European Medicines Agency's priority medicines or PRIME scheme will not necessarily lose their eligibility to be in the scheme if a competitor developing a product targeting a similar unmet medical need gets to market first.

"The availability of a new treatment in an area of unmet medical need does not necessarily mean the unmet medical need has been completely fulfilled," the EMA told the *Pink Sheet*. "In view of the PRIME criteria and definitions used, if a new treatment becomes available in an area of unmet medical need, a PRIME product may still have the potential to bring a major therapeutic advantage over existing therapies".

There are various reasons a PRIME-designated product may no longer meet the eligibility criteria that led to it being included in the first place. "Over the course of drug development, it can be expected that some products granted PRIME support will no longer meet the eligibility criteria (eg further to data derived from confirmatory study or availability of other therapies fulfilling the unmet medical need)," the EMA said.

MULTIPLE PRODUCTS

The fact that a product targeting a specific unmet medical need is in PRIME does not prevent other companies from applying to secure the coveted designation for products targeting the same or similar unmet need.

It's "nice and simple", according to Robert Hemmings, a senior official at the UK regulator, the MHRA, and chair of the EMA's scientific advice working party. There's an "equal playing field" for all products that apply for PRIME designation, Hemmings said. "Other products that are under development or evaluation are considered to not yet fulfil the unmet medical needs… so the unmet need exists even if you are second or third or fourth in the race."

Hemmings was speaking on May 19 at a meeting the EMA hosted at its headquarters in London to mark the first anniversary of PRIME and experience with the scheme since it was launched in March 2016. *(Also see "EMA's PRIME A Year On: Hits And Misses When It Comes To Applications" - Pink Sheet, 24 May, 2017.)(Also see "Accelerated Assessment Decision 'Imminent' For Two Products In EMA's PRIME Scheme" - Pink Sheet, 19 May, 2017.)*

Five new products were accepted onto the scheme last week, bringing to 25 the total number of products to have been granted PRIME designation since the scheme was launched. Just one has been withdrawn. *(Also see "Blood Disorders Overtake Cancer On EMA's PRIME Scheme" - Pink Sheet, 27 Apr, 2017.)*

"Medicines eligible for PRIME support shall target conditions where there is an unmet medical need and demonstrate the potential to address to a significant extent the unmet medical need for maintaining and improving the health of patients in the EU, for example, by introducing new methods of therapy or improving existing ones," the EMA noted.

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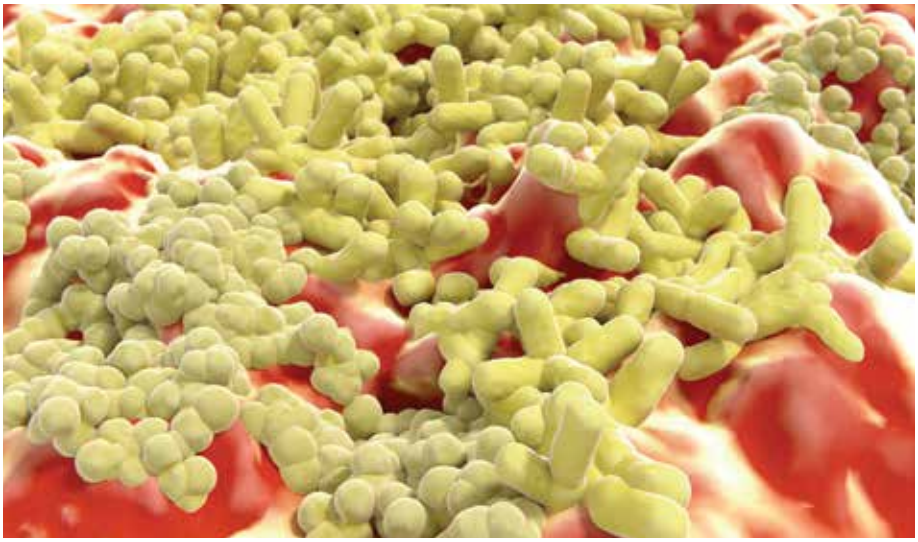
Why Still Nothing For AMR? EMA Asks PRIME Scheme Applicants

NEENA BRIZMOHUN neena.brizmohun@informa.com



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The EMA wants applicants for its PRIME scheme to target antimicrobial resistance

The European Medicines Agency is encouraging developers of antimicrobial resistance (AMR) therapies to consider applying for designation under its priority medicines (PRIME) scheme for getting medicines for unmet medical needs to patients faster.

There have been around 100 applications for PRIME so far, but none of them are for an investigational product for AMR, according to Robert Hemmings, chair of the EMA's Scientific Advice Working Party. Developing therapies for the AMR problem "is an area that I personally would really like to support," he said of future PRIME applications in the infectious diseases area.

Hemmings was speaking on May 19 at a meeting the agency hosted at its headquarters in London to mark the first anniversary of PRIME and experience with the scheme since it was launched in March 2016.

It is a puzzle why none of the PRIME applications have targeted AMR, according to the EMA's head of scientific and regulatory management, Jordi Linares Garcia.

"I don't have a convincing answer," Linares told the *Pink Sheet* during a press briefing at the meeting. "The unmet medical need is undeniable."

"We thought we were offering a good platform for discussion" for companies developing drugs for AMR, Linares said. PRIME is designed to provide medicines developers with early and proactive support from the EMA to optimize the generation of robust data on a medicine's benefits and risks. PRIME-designated products are also potentially eligible for accelerated assessment.

> "The unmet medical need is undeniable" – EMA's Jordi Linares Garcia.

Asked why no AMR drug developers had come forward, Linares ventured that perhaps the incentive offered under PRIME was not enough to offset the concerns sponsors have about being able to obtain reimbursement in the EU member states. "But this is just speculation," he stressed.

Nevertheless, Linares remains upbeat about the situation. "This is an area where we expect in the future we will see interesting applications that we can accept in PRIME," he said.

Statistics released by the EMA to date show that the agency processed 96 PRIME applications between April 2016 and April 2017, granted PRIME designation to 20 of them, and rejected 71 (the remaining five applications were deemed to be out of scope of the scheme). An additional five investigational drugs were accepted on the scheme last week, according to Linares, though the EMA has not yet updated its publicly available statistics with these new products.

Seven of the applications that the EMA has received fall under PRIME's category of infectious diseases, but none of these have made it onto the scheme, although an application for a product for Ebola has been granted eligibility to PRIME under the vaccines category.

All seven infectious disease applications, which targeted such things as antifungals, HIV and Clostridium difficile, passed PRIME's criterion of unmet medical need, Linares noted. One of the reasons for applications being rejected was that they were too late in development to be eligible for PRIME, he added.

As for the overall fight against AMR, last September the UN adopted a Political Declaration at its high-level meeting on AMR in which UN member countries pledged to strengthen health systems, monitor antibiotic usage in both humans and animals, and mobilize resources for R&D into new antimicrobial drugs, vaccines and diagnostics. *(Also see "UN Countries Make Bold Pledges On AMR, Including Funding For R&D Into New Drugs and Diagnostics" - Pink Sheet, 21 Sep, 2016.)*

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Biomarker-Led Claim Is Small Step For Merck's Keytruda, Giant Leap For Cancer Indications

MARY JO LAFFLER maryjo.laffler@informa.com

FDA's approval of **Merck & Co. Inc.**'s *Keytruda* for use in any patient with a solid tumor with a particular genetic mutation is the first of its kind and could herald a new approach to treating cancer.

The agency announced the accelerated approval of Merck's PD-1 inhibitor Keytruda (pembrolizumab) May 23, noting "this is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated."

The new indication, Keytruda's ninth, is for adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and specifically in colorectal cancer patients with the biomarkers that have completed earlier lines of treatment (*see box*). Labeling cautions that pediatric patients with MSI-H central nervous system (CNS) tumors have not been adequately studied.

"This is an important first for the cancer community," Richard Pazdur, director of FDA's Oncology Center of Excellence, said in FDA's statement on the approval. "Until now, the FDA has approved cancer treatments based on where in the body the cancer started – for example, lung or breast cancers. We have now approved a drug based on a tumor's biomarker without regard to the tumor's original location."

MORE TO COME?

Multi-histology or tissue-agnostic approaches have mostly been viewed as a mechanism for low-incidence tumors, but in this case it also means finding the subpopulation more likely to respond to immunotherapy in a tumor type that generally hasn't been receptive.

"Basket" trials that assign patients to therapy based on molecular signatures are an increasingly popular clinical trial design, with high-profile efforts like the National Cancer Institute's MATCH study, the American Society of Clinical Oncology's TAPUR trial and **Novartis AG**'s SIGNATURE protocol. *(Also see "Genomics-Driven Trials Built To Be Fast And Flexible" - Pink Sheet, 21 Sep, 2015.)*

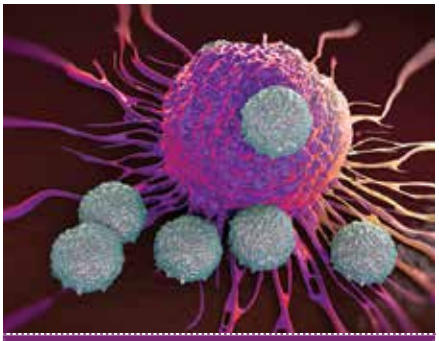
But while their ability to speed research and improve targeting is clear, the regulatory path has been less certain. The closest example was the approval of Novartis' *Gleevec* based on a histology-independent trial that included more than 40 uncommon cancers with high unmet need; the FDA issued four indications for specific tumor types from that pivotal trial. *(Also see "Gleevec: A Groundbreaking Example" - In Vivo, 27 May, 2014.)*

The Keytruda approval clearly demonstrates FDA's openness to this approach. With a recent spate of breakthrough designations (BTDs), including for Keytruda's new indication, the agency has guided a few drugs through late-stage development for treatment of cancer patients based on molecular signatures, as opposed to the traditional paradigm focused on tissue of origin.

Keytruda first received a BTD for MSI-H colorectal cancer, then added another for MSI-H non-colorectal cancers.

Loxo Oncology Inc.'s larotrectinib and **Ignyta Inc.**'s entrectinib both hold BTDs for tissue-agnostic indications. Loxo's larotrectinib, a selective inhibitor of the Trk family of receptor tyrosine kinases, is currently in the Phase II NAVIGATE basket trial, potentially supporting a late 2017 or early 2018 NDA filing for NTRK fusion-positive solid tumors. Ignyta's entrectinib, which also targets the Trk family, has the Phase II STARTRK-2 basket trial under way with a possible 2018 NDA filing for NTRK fusion-positive solid tumors.

Loxo's larotrectinib is also in Phase I studies for sarcoma, while Ignyta's entrectinib is in Phase II trials for NSCLC and colorectal cancer as well.



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NEW INDICATION

Microsatellite Instability-High Cancer: for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient

- solid tumors that have progressed following prior treatment in patients who have no satisfactory alternative treatment
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

- Limitation of Use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established.

Datamonitor Healthcare analyst Jared Wolff told the *Pink Sheet* that the approval for Keytruda "certainly sets a precedent that it can be done."

HOW MERCK GOT IT DONE

Merck's approval was based on a collection of patients with MSI-H or dMMR solid tumors from across five uncontrolled, single-arm clinical trials. (*See chart below.*)

Some of the trials were solely in biomarker-selected populations, but in other trials a subgroup was built of patients who tested for MSI-H or dMMR after treatment began. In total there were 15 cancer types among 149 biomarker-positive patients across the five trials; the most common cancers were colorectal, endometrial and other gastrointestinal cancers, FDA noted.

Of the 149 patients who received Keytruda in the five trials, 39.6% had a complete or partial response and the response lasted six months or more in 78% of those patients.

Merck is conducting additional studies in patients with MSI-H or dMMR tumors to meet the accelerated approval requirements for confirmatory trials.

Both MSI-H and dMMR mutations affect the natural processes of DNA damage repair inside the cell. According to FDA, the biomarkers are most commonly found in colorectal, endometrial and gastrointestinal cancers and less commonly in other cancers, including breast, prostate, bladder and thyroid gland. "Approximately 5% of patients with metastatic colorectal cancer have MSI-H or dMMR tumors," the agency reported.

Bristol-Myers Squibb Co.'s PD-1 inhibitor *Opdivo* (nivolumab) is under review at FDA for MSI-H colorectal cancer only with an Aug. 2 user fee goal. *(Also see "Keeping Track: Teva's Austedo Clears US FDA, Merck Sitagliptin CV Outcomes Labeling Draws Complete Response" - Pink Sheet, 7 Apr, 2017.)*

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Additional reporting by Lucie Ellis (lucie.ellis@informa.com) and Bridget Silverman (bridget.silverman@informa.com)

Keytruda MSI-H Trials

STUDY	DESIGN & PATIENT POPULATION	NUMBER OF PATIENTS	MSI-H/DMMR TESTING	DOSE	PRIOR THERAPY
KEYNOTE-016 NCT01876511	prospective, investigator-initiated 6 sites patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	CRC: ≥ 2 prior regimens Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	prospective international multicenter CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- antiVEGF/EGFR mAb
KEYNOTE-012 NCT01848834	retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	prospective international multicenter enrollment of patients with MSI-H/dMMR non-CRC retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19 l	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
TOTAL		**149**			

Source: Keytruda labeling

Woodcock Wants Rapid Regulatory Policy Development

DERRICK GINGERY derrick.gingery@informa.com

The US FDA wants to speed up its policy-making process to better keep up with the speed of scientific advances affecting drug reviews.

Center for Drug Evaluation and Research Director Janet Woodcock said guidances and other policies need to be written faster and more efficiently to ensure drug sponsors receive the most up-to-date advice.

Janet Woodcock, Center for Drug Evaluation and Research Director

"We have to figure out a way to have rapid policy development," she said during the recent Drug Information Association-FDA Statistics Forum. "How do we get rapid statistical policy, rapid guidance out, because the science is changing very fast and we need to figure out a way to keep up with that."

Woodcock added that a portion of that goal includes streamlining FDA processes for making policy prescriptions.

"We, internally, really need to work on efficiency with all these assignments," she said. "We at FDA really need to keep focused on the drug development pathways, how do we think about the armamentarium, how do we think about the disease, how do we think about the advice that we give."

The idea fits with the message of new FDA Commissioner Scott Gottlieb, who wants agency staff to share best practices in order to increase efficiency. *(Also see "Gottlieb Promotes 'Bottom-Up' Review To Increase FDA Efficiency, Consistency" - Pink Sheet, 6 Apr, 2017.)*

Woodcock did not hint at what may encompass rapid policy development. But it seems possible any changes could coincide with her reorganization of the Office of New Drugs.

Following the departure of long-time director John Jenkins, Woodcock took over OND temporarily and has been talking with staff about changes to make reviews more uniform. *(Also see "CDER Director Woodcock Plans Changes To Drug Reviews During OND Transition" - Pink Sheet, 6 Mar, 2017.)*

If FDA can provide faster policy development, it may come in the form of formal meeting advice to sponsors, rather than guidance. The agency and industry embraced an increase in formal meetings both before application submission and during the review for complex generics, as well as biosimilars and new drugs, to help speed development.

Lawmakers also are interested in expanding the concept of formal meetings during review to generics looking to enter markets with little or no competition. *(Also see "Breakthrough-Style Program For ANDAs Added To House User Fee Bill" - Pink Sheet, 18 May, 2017.)*

CLEARANCE PROCESS MAY REMAIN A BARRIER

Making guidance available to the public faster still may prove difficult, in part because a portion of the process is out of FDA's control.

Once a draft guidance is completed, it can be weeks or months before it is published as it winds through the clearance process, where HHS and White House staff review it.

Indeed, an anticipated biosimilars guidance is among the documents now navigating the process. Lisa LaVange, director of the CDER Office of Biostatistics, said during the conference that draft guidance on statistical approaches for evaluating analytical similarity data to show biosimilarity was in the clearance process.

Draft guidance on meta-analysis of randomized control trials to evaluate the safety of human drugs and biologics also is awaiting clearance, LaVange said.

Both documents were included on CDER's 2017 guidance agenda.

FDA released guidance on biosimilar interchangeability in January. *(Also see "Interchangeability: FDA Sets 'Stringent' Standard On Design Differences" - Pink Sheet, 24 Jan, 2017.)* It was among the dozens of guidances and other documents the agency released in the waning days of the Obama Administration. *(Also see "FDA's Document Dump: Guidance Release Skyrockets Ahead Of Trump's Arrival" - Pink Sheet, 22 Jan, 2017.)*

FDA also is working on several guidances intended to help sponsors better incorporate patient-reported outcomes into clinical trials that were mandated by the 2016 21st Century Cures Act *(Also see "Woodcock, Califf Give Thumbs Up To Certain 21st Century Cures Provisions" - Pink Sheet, 14 Dec, 2016.)*.

The prescription drug user fee reauthorization also requires additional work on the patient-focused drug development effort launched as part of the 2012 program renewal. *(Also see "You Just Have To Wait: FDA Can't Hurry PDUFA VI Guidances" - Pink Sheet, 15 Aug, 2016.)*

PROGRESS DEPENDS ON ADOPTION, MULLIN SAYS

Theresa Mullin, director of CDER's Office of Strategic Programs, said during the conference that a major portion of the patient data and statistics policy development will include putting the new standards into practice.

Mullin said more training and increased communication will be necessary to build confidence in the new approaches.

"I think the pace of our progress here, real progress, not just talking in conferences, is going to depend on how well we can get to clear definitions of these various terms and widely understood definitions that we're using, whether it be patient area or real-world evidence or any of them, that we have clarity around definitions, that we have data standards that support and work with those definitions," she said.

Also important to future use of the standards will be the ease that data can be incorporated into drug labeling as new uses.

The Friends of Cancer Research has called for more discussion on how to add quality clinical experience data to labels when a supplemental NDA submission is not feasible.

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US FDA Urged To Rethink Warning Letters To Avoid 'Collateral Damage'

SUE SUTTER sue.sutter@informa.com

FDA should re-evaluate when it issues warning letters, and the language it uses within them, given the collateral damage they can cause for pharmaceutical manufacturers, industry attorneys said at the recent Food and Drug Law Institute (FDLI) annual meeting.

During a panel discussion on Center for Drug Evaluation and Research (CDER) activities and priorities, industry attorneys questioned whether the agency considers late-submitted responses to adverse inspection reports before issuing warning letters.

They further asserted that that the language used in warning letters does not always match how FDA characterizes them in court, and that the agency appears, in some cases, to be establishing new regulatory requirements through such letters.

The issues raised by the legal experts suggest a growing concern about the impact that warning letters can have on a manufacturer's operations and reputation.

"Today there are significant collateral consequences associated with receiving a warning letter from the FDA that I'm not sure the FDA itself is aware of," said Sheldon Bradshaw, a partner at King and Spalding.

Whether industry's concerns about FDA warning letter practices are mitigated by the recent reorganization of the agency's field force under the program alignment initiative remains to be seen. *(Also see "FDA Aligns New Pharmaceutical Inspectorate Into Six Divisions" - Pink Sheet, 16 May, 2017.)*

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> "Industry attorneys suggest a growing concern about the impact that FDA warning letters can have on a manufacturer's operations and reputation.

ADDRESSING DEFICIENCIES TAKES TIME

At the outset of the FDLI session, CDER Deputy Director for Science Operations Richard Moscicki made clear he would be limited in how much he could talk about, given the recent change in administration.

"This is kind of an awkward moment," he said. "The administration really hasn't had a chance yet to fully evaluate its position on many of the policy issues that we're dealing with at the agency and at CDER, and so I'm going to have to avoid some of our discussions that might be of most interest to you around such policy issues."

That caveat notwithstanding, attorneys and consultants on the panel brought to Moscicki's attention various issues of concern to the pharmaceutical industry, such as generic drug manufacturers' desire to receive advance notice ahead of an abbreviated new drug application approval. *(Also see "Generic Drug Sponsors Seek Advance Notice Of Approvals From US FDA" - Pink Sheet, 16 May, 2017.)*

Concerns about FDA's warning letter practices were a common refrain from panelists, particularly regarding what information FDA considers before it issues a citation for current Good Manufacturing Practice deficiencies.

Cathy Burgess, a partner at Alston and Bird, said that in some recent letters FDA stated it had reviewed in detail a firm's initial response to a Form 483 report but only acknowledged receipt of subsequent correspondence from the facility owner.

Many establishments are not able to complete all of their corrective actions within the 15-day period prior to submission of the initial 483 response, she said, adding, "It takes time."

"For that reason, companies will then report to FDA on corrected actions that have been completed later in the process," she said. "It seems to me that were FDA not to take any of that information into consideration, at the very least creates a disincen-

tive to report to FDA, but could in fact create a disincentive to make the corrective actions" because companies will just wait until they get the warning letter.

"I think it would be useful for the agency to maybe reach some sort of understanding with industry about how establishments can get credit for doing that work, taking corrective actions voluntarily, before receiving a warning letter," Burgess said.

Moscicki said CDER's Office of Compliance reviews all responses regardless of whether they come in during or after the 15-day period.

"It's not just an acknowledgement of receipt," he said of late-submitted responses. The warning letter language "may reflect the fact that this is not just CDER, this is [an] agency-wide thing about the 15 days, and so the language that I think everybody in the agency had come to comfort with was the word acknowledge. I assure you that CDER is reading those and looking at them and they were considered in the process."

WARNING LETTERS SPAWN LEGAL ACTIONS

Bradshaw, a former FDA chief counsel, confirmed there is an agency-wide directive that any responses after 15 days may or may not be considered for purposes of deciding if a warning letter is warranted. However, he suggested FDA should reconsider this approach due to the adverse consequences that the mere issuance of a warning letter can have for a manufacturer trying to address a problem.

"Most class action lawsuits against FDA-regulated companies start with the plaintiffs going into court and holding up the warning letter as evidence or proof that the company is also in violation of some state law that piggybacks on the Food, Drug and Cosmetic Act," Bradshaw said, adding that the letters also serve as the basis of actions brought by state attorneys general and shareholders.

Warning letters now have significant repercussions, Bradshaw said, and it is frustrating for companies "when a warning letter raises an issue that may not have been addressed in the 15-day response to the agency but was, in fact, raised in a subsequent follow-up to the agency but just wasn't considered.

> "Warning letters are much more significant than they were in the past." – King and Spalding's Bradshaw

And now … results in all of these other actions that are going to impact the company. Warning letters are much more significant than they were in the past."

DEFENDING THE 15-DAY RESPONSE WINDOW

Speaking from the audience, Donald Ashley, director of CDER's compliance office, said the agency is "obviously well aware" of the impact of warning letters on manufacturers and considers them very carefully.

"The policy of the agency is to require a 15-day turnaround time for the response to a 483. There's a balance there between you have to have a deadline at some point if we're going to come to a resolution on the issue," he said. "In CDER compliance, we carefully review all of the supplemental responses that come in prior to the issuance of a warning letter."

Ashley also said the compliance office is working to speed up the process for issuing warning letters.

"We've made great strides in actually cutting down the time to issue one," he said. "In 2015, the average time for CDER to issue a warning letter was something like 11 months from the date the EIR [establishment inspection report] was received. And for the first three months of 2017, for example, we've already issued as many warning letters and the average time is around six months."

With its efforts to reduce the warning letter turnaround time, the agency is moving closer to the goals laid out in the negotiated agreement to reauthorize the Generic Drug User Fee Act (GDUFA), Ashley said. Under the GDUFA II agreement, by October 2018 FDA will communicate to the facility owner a final inspection classification that does not negatively impact approvability of a pending application within 90 days of the inspection's end.

The industry is "very interested in seeing that within 90 days from the end of an inspection that you're going to know what your facility classification is," Ashley said. "We would never be able to meet that 90-day goal for the facility classification if we were doing continuous review and response to industry as it would come in."

"We weigh very carefully all of that information and we take the issuance of a warning letter very seriously knowing the impact that it has," Moscicki said. "But we do want warning letters to have an impact."

LANGUAGE INCONSISTENT WITH LEGAL POSITIONS

Bradshaw suggested that the language in warning letters sometimes appears inconsistent with what the agency says in court about the communication vehicle.

"Whenever companies receive a warning letter and run into court to try to seek a declaratory judgment that in fact notwithstanding the warning letter they're in compliance with the law, the FDA always comes in and, correctly in my view … [says] that warning letters do not represent final agency action and there's lots of language that the FDA uses in court filings," Bradshaw said.

He urged FDA to "go back and look at the statements that the agency has made in court describing warning letters and just making sure that … the language in warning letters is consistent with how the FDA then describes warning letters in federal court. I think there's sometimes a bit of a disconnect between those two."

LETTERS REFLECT REGULATORY CREEP

Attorneys also expressed concerns about regulatory recommendations creeping into warning letters as FDA requirements.

For example, although FDA is not requiring companies to adopt continuous manu-

facturing approaches, "I think that there is much concern, particularly in the generic industry, about that creeping in as a current Good Manufacturing Practice and ultimately … becoming a requirement even if the FDA never says that it is," Bradshaw said.

"As my friends in CDER often remind me, the 'c' in cGMP stands for current," Bradshaw said. "I've often gone back and forth with the agency where there's been an inspectional observation in a 483 for something that is only recommended by the agency in a guidance document. And their response back is, 'Sure guidance is nonbinding, and is only making recommendations, but the GMPs are cGMPs and we think this is the current approach and as a result you're going to get an inspectional observation.'"

"There are lots of areas where the FDA does not actually require anything because what they're asking industry to do is laid out in a guidance, but yet over time these end up as inspectional observations and can be the source of a warning letter," he said.

Sometime warning letters even go so far as to suggest agency expectations beyond those laid out in existing guidance, Burgess said.

"There's now language, particularly in the data integrity language that we see in warning letters, that goes beyond what's in the draft guidance," she said. "The standards for what a data integrity program ought to look like are now not really as explicit in the draft guidance as they are in other establishments' warning letters. So industry really has to be careful and look everywhere to make sure that you understand how the agency is interpreting what the 'c' means in current Good Manufacturing Practices."

CDER Deputy Director for Science Operations Richard Moscicki

> CDER carefully weighs all responses and takes issuance of a warning letter "very seriously knowing the impact that it has, but we do want warning letters to have an impact." – FDA's Moscicki

Data integrity issues at foreign active pharmaceutical ingredient manufacturers accounted for some of the more than two-fold increase in drug GMP warning letters issued in 2016. *(Also see "FDA GMP Warning Letters Review: Rate Soared In 2016 On Sterility And Data Integrity Concerns" - Pink Sheet, 25 Apr, 2017.)*

Moscicki suggested the program alignment initiative establishing a dedicated pharmaceutical inspectorate may help address some of industry's concerns related to inspectional findings and warning letter practices. The new organization took effect May 15.

"As we move forward with program alignment and closer working relationship between the centers and the inspectors and the greater ability to have more communication and more quick communication between our inspectorate and the centers, [that] may help alleviate some of what you're concerned about," he said.

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Commission Delays EU GMP Guide For Advanced Therapies To Address Inspectorates' Concerns

VIBHA SHARMA vibha.sharma@informa.com

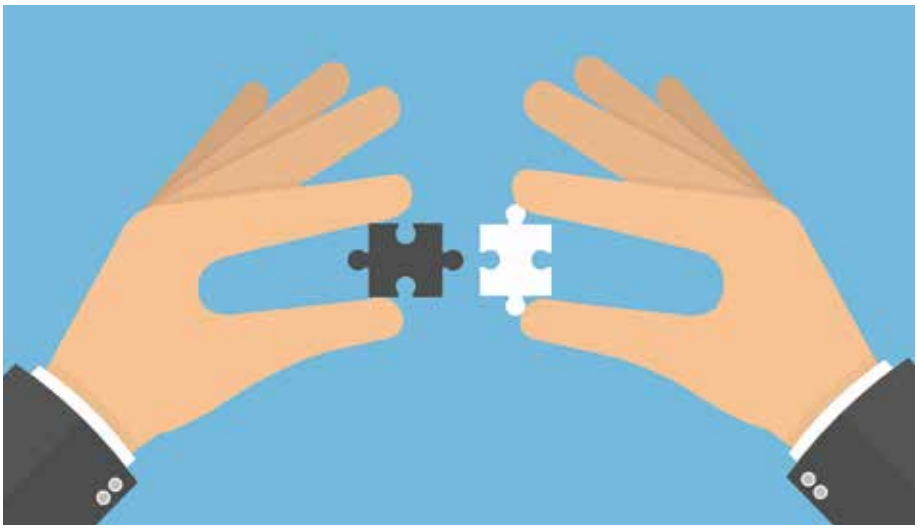
The European Commission says it has made "good progress" on resolving concerns raised by regulatory authorities participating in the international Pharmaceutical Inspection Co-operation Scheme (PIC/S), and some other stakeholders, about its draft guideline on good manufacturing practice requirements for advanced therapy medicinal products (ATMPs).

The guideline – which is eagerly awaited by the pharmaceutical industry – was initially due to be finalized on April 26, but the Commission did not go ahead with this as it is "committed to addressing all views and concerns before the adoption of the [final guidance] document," it told *the Pink Sheet*.

PIC/S and some other stakeholders – like the Alliance for Regenerative Medicine, a global advocacy group for regenerative and advanced therapies – recently raised serious concerns about the Commission's proposed approach to GMP for ATMPs. PIC/S is especially concerned that the Commission's proposal would not only lower EU GMP standards for ATMPs, thereby putting patients to risk, but that it would result in the EU and PIC/S diverging on this topic in a way that may be difficult to reconcile in the future. *(Also see "Commission Defends GMP Guide For ATMPs As PIC/S Cautions Against Divergence" - Pink Sheet, 21 Mar, 2017.)*

The Commission, in response, said that it had carefully analysed the concerns raised by PIC/S and offered clarifications on the points raised as well as on the content of the draft guideline. In addition, it said it had offered PIC/S the possibility to hold a discussion on this subject. *(Also see "European Commission To 'Explain And Discuss' Contentious GMP Guide For ATMPs" - Pink Sheet, 2 May, 2017.)*

PIC/S told the *Pink Sheet* that it is currently in the process of assessing the latest reply received from the Commission, and it would aim to work in co-operation with the Commission on finalizing the draft guideline. This, it said, is in line with PIC/S' mission to lead the international development, implementation and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of medicinal products.



PIC/S is especially concerned that the commission's proposal would not only lower EU GMP standards for ATMPs, but would result in the EU and PIC/S diverging on this topic in a way that may be difficult to reconcile in the future.

The pharmaceutical industry, meanwhile, is disappointed that the guideline has not been published yet, but said that it was supportive of the Commission's efforts to address any remaining concerns before finalizing this key guideline. "We remain keen to see the Commission guideline on GMP for ATMPs published sooner rather than later," Barbara Freischem, executive director of the European Biopharmaceutical Enterprises (EBE), told the *Pink Sheet*.

During the public consultation process on the guideline, the EBE, along with the European Federation of Pharmaceutical Industries and Associations (EFPIA), had highlighted the need for all stakeholders to be on the same page. "In our comments we had suggested to the Commission that a stakeholder meeting should be arranged with all interested parties to achieve that [consensus]," Freischem added.

The commission said it would aim to finalize the guideline "as soon as possible while taking all views into account and following the necessary procedural steps for adoption. The exact timing cannot be anticipated at this moment."

The GMP guideline for ATMPs has been in draft format for nearly two years. It has already undergone two rounds of public consultation – first from July 23 to Nov. 12, 2015, and then from June 28 to Sept. 26, 2016.

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

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OTC Monograph User Fees Totaling $22m To $34m Floated In Senate Discussion Draft

MALCOLM SPICER malcolm.spicer@informa.com

A proposal to raise $22m to $34m in annual user fees from OTC manufacturers – primarily from facility registrations – is contained in a discussion document being circulated by Sens. Johnny Isakson, R-GA, and Bob Casey, D-PA.

Fees would also be raised when companies request changes via the monograph system, which would be recast into a two-tier program. *(Also see "Two-Tier OTC Monograph Approach Could Come With User Fee Revamp" - Pink Sheet, 19 May, 2017.)*

While the current proposal does not detail how much would be raised from registering manufacturing facilities with FDA versus requesting monograph changes, the majority of the funds are anticipated to come from the former. Some industry leaders, including the Consumer Healthcare Products Association, view facility fees as spreading the financial responsibility more broadly and creating a more predictable funding source than monograph requests.

In return, industry would see changes to streamline the monograph system, which governs when ingredients are recognized as safe and effective for the US OTC market and which medical conditions those ingredients can be claimed to address. The system has gotten so bogged down and cumbersome that FDA drug center chief Janet Woodcock called it "frozen in amber" at a recent OTC industry conference.

The possibility of new user fees to support monograph changes has been discussed for a least a couple years and the Isakson/Casey discussion draft contains provisions negotiated between FDA and OTC industry stakeholders, but the specific details have not previously been disclosed.

The proposal would move forward by being attached to legislation already moving through Congress to reauthorize FDA's existing user fee programs.

The Senate Health, Education, Labor and Pensions Committee passed and the House Energy and Commerce Health Subcommittee moved to full committee separate versions, S. 934 and H.R. 2430, of the FDA Reauthorization Act (FDARA). The must-pass legislation would continue for five years the agency's existing user fee programs for drugs and medical devices. The programs would no longer stand if Congress does not pass a reauthorization bill by Sept. 30, the end of the federal fiscal year. *(Also see "Breakthrough-Style Program For ANDAs Added To House User Fee Bill" - Pink Sheet, 18 May, 2017.)*

Time is limited, however, for adding an OTC component and completing work on the overall user fee package.

"The time window is short and we certainly hope that people take this seriously and it will be considered," Woodcock said in opening remarks to the Consumer Healthcare Products Association's Regulatory, Scientific and Quality conference May 11-12 in Rockville, Md.

"We've been negotiating and engaging with [industry] via ongoing monograph reform discussions for quite some time," she noted.

The majority of funds raised by OTC user fees are anticipated to come from registering manufacturing facilities.

At the event, Barbara Kochanowski, CHPA's senior vice president, regulatory and scientific affairs, acknowledged that some on Capitol Hill say OTC monograph reform and user fee legislation has "missed the window" this year while others say the "window's still open."

"As long as there is a legislative champion there is a possibility this can happen," Kochanowski said.

Adding the changes to legislation reauthorizing FDA's existing user fee program likely will take a champion in a House and Senate conference committee to work out differences in the two chambers' bills.

Kurt Karst, a food and drug lawyer following FDARA discussions in Congress, noted that the OTC issues were not mentioned before

the Senate HELP Committee and the House Health Subcommittee voted on the separate bills.

"That being said, if there's a conference committee, there may be an attempt to add it there. If not now, it could be five years … but I suspect that there would be an effort beforehand," said Karst, a director at Hyman, Phelps & McNamara P.C. in Washington.

RULEMAKING PROCESS STALLED MONOGRAPH CHANGES

FDA launched the monograph program, following congressional authorization, in 1972 as a system for allowing OTC ingredients generally recognized as safe and effective for their intended uses to remain available and for offering drug firms and other parties a process for proposing additions of more ingredients or indications. *(Also see ""No End In Sight" For Completing OTC Monographs – CDER Director Woodcock" - Pink Sheet, 26 Mar, 2014.)*

The monograph includes essentially a menu of ingredients and formulations that can be used in drugs for certain indications, and what has become a byzantine maze of rulemaking that must be navigated for any addition to change, no matter how small or how urgently needed, to any part of the monograph. In contrast, of course, FDA need not go through formal rulemaking to approve new prescription drugs.

The monograph program has been stalled for much of its 45 years and FDA and industry stakeholders identified reforming the program as a nonprescription sector priority well before they began negotiations on a proposal in June 2016.

"The pace of completing the monograph system has really come almost to a halt," Woodcock said at the CHPA event. "There's no innovation really possible in an area that would be a significant innovation. We really have challenges in safety, because of our inability to respond quickly when safety problems arise."

When the monograph system launched, rulemakings for all federal agencies could be completed much sooner. However, the introduction of notice-and-comment periods and of Office of Management and Budget reviews added layers of complexity and years to the timeline in proposed rulemakings.

With rulemaking "the heart and soul of" the monograph process, the time has passed when "things just moved along," Kochanowski said. "We haven't seen that in a long, long time."

Moving the monograph system from a rulemaking to administrative process, conducted within FDA without review by OMB, should produce a final decision within two years of a proposal's filing with the agency.

"Even much faster in the case of safety issues or where there's a need for very quick changes," Kochanowski said.

REFORM COMES AT A COST FOR ALL

FDA opened a docket for comments on monograph reform two years before a separate docket about user fees to pay for its work, and it's been clear since that the monograph program would not improve without additional funding. *(Also see "All Roads For OTC Policy Improvements Lead To User Fees, FDA Suggests" - Pink Sheet, 7 Sep, 2016.)*

"It would be very nice if this all came for free," Kochanowski said, adding, "FDA would probably like even more money than we've come to an agreement on and industry would like to pay less."

> "Probably many folks at FDA and people who have been in the industry for many years may not even be aware of all the nuances in the OTC monograph." – FDA's Teresa Michele.

While some in the industry supported basing user fees only on monograph proposals, fees linked to manufacturing facility registration also are needed to assure that all firms making products approved through monograph additions or changes will bear some of the program's costs.

"Our objective is to spread the payload as widely as possible, as broadly as possible, so that everyone with a stake in OTC monograph products is contributing. We have no doubt that this will continue to be discussed going forward," Kochanowski said.

Additionally, annual facility registration fees can be calculated in advance. "We need to offer a predictable resource of revenue and that is the thinking behind the facility fee model," she said.

The FDA and industry agreement detailed in the discussion draft calls for monograph drug firms to pay totals of $22m to $34m annually over the five-year authorization of the program and for FDA's direct appropriation for all of CDER's OTC programs to grow from $8m to $12m during that period.

"We could find that we asked a lot more of FDA than we agreed to pay for and we could find that we need other things that we haven't talked about," Kochanowski said.

In addition to determining whether the monograph user fee totals are sufficient, FDA will measure the effectiveness of the program on its success in adding staff infrastructure needed to add to support the work as well as on the number of additions or changes made to the monograph.

Teresa Michele, director of CDER's Office of Nonprescription Drug Products, explained that two years are needed for training staff in the office's programs and policies. "Probably many folks at FDA and people who have been in the industry for many years may not even be aware of all the nuances in the OTC monograph," Michele said.

FDA would be required to provide guidance on multiple components of the changes and an annual letter to industry stating its goals for the program.

The infrastructure changes would include adding a section on monograph requests to FDA's website and converting the rules it has published for monographs into administrative orders. "Creating a new world and a new language for all of us to talk about," Kochanowski said.

From the editors of The Tan Sheet. Published online May 25, 2017

Two-Tier OTC Monograph Approach Could Come With User Fee Revamp

MALCOLM SPICER malcolm.spicer@informa.com

Industry could have two tracks for seeking changes to OTC products marketed under the US monograph system: one for adding new ingredients or medical conditions treated by those ingredients, which would be eligible for exclusivity when clinical trials are required, and another for other types of changes.

The approach is proposed in a discussion draft of legislation to create a user fee program for OTC products, authored by Sens. Johnny Isakson, R-GA, and Bob Casey, D-PA. The new approach, intended to encourage adding new ingredients to monographs and speeding FDA reviews, would be the return on investment for paying user fees, which could total up to $34m per year. *(Also see "OTC Monograph User Fees Totaling $22m To $34m Floated In Senate Discussion Draft" - Pink Sheet, 19 May, 2017.)*

The plan would be added to pending legislation to reauthorize existing drug and medical device user fee programs, and, like those programs, reflects FDA/industry agreement.

Similar to the Sunscreen Innovation Act Congress passed in 2015 to encourage adding new ingredients to the OTC sunscreen monograph, the discussion draft Sens. Isakson and Casey circulated May 10 proposes deadlines for FDA reviews for the other monograph categories.

Monograph proposals, under the senators' draft, would become "requests" and firms or other parties submitting them would be "requestors," rather than sponsors, as FDA uses to identify the sources of new drug application proposals.

Monograph requests would be categorized as tier 1, which would develop monographs for new ingredients or add new medical conditions to existing monographs, and tier 2, which would be for making changes to approvals for existing ingredients, such as updates to safety updates to product labeling.

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PROGRESS BY THE DASHBOARD LIGHT

Targeting the lack of transparency in the current monograph system, the proposal agreed to by the agency and the industry includes a requirement that FDA at least once annually post an online "dashboard" about its monograph plans.

Barbara Kochanowski, CHPA's regulatory and scientific affairs chief, anticipates that industry stakeholders might be underwhelmed by an FDA exercise in publishing its goals. The monograph dashboard, though, won't be a narrowly targeted unified agenda by another name.

"We don't envision this to be a unified agenda type dashboard that we all look at and go, 'OK maybe.' This is really going to be FDA's best estimate of priorities on when they intend to attack different ingredients," Kochanowski said.

FDA would have authority to request human clinical trials for tier 1 requests. If it does, the manufacturer would be eligible for up to two-years market exclusivity. This resembles a component of the agency's rule for Rx-to-OTC switch applications that allows three years of exclusivity for proposals that must include clinical trial data.

"That would mean that once the conditions are changed the requestor would have exclusive rights to those new conditions for a period of time," said Greg Collier, regulatory and safety director for **Procter & Gamble Co.**, said in a presentation at a recent Consumer HealthCare Products Association conference.

The tier 2 category is not yet defined as clearly as tier 1, though requestors will pay fees for both types. "We're going to actually grow into this as an industry and so

will FDA. But when we start those tier 2 innovations will be clearly spelled out and everything else will be tier 1 innovations," Collier said.

According to the discussion draft, the user fees for requests will be $500,000 for tier 1 and $100,00 for tier 2. Fees will be waived for requests to change labeling to improve safe use of an ingredient, and different amounts of the fees will be refunded when a requestor withdraws an "OTC monograph order request" (OMOR) and when a request is re-classified from tier 1 to 2.

FDA would have to conclude reviews in less than two years, under the proposal. The clock would start with FDA having two months to decide whether a request will be reviewed or needs additional information. The agency would have 10 months to decide whether to approve or deny tier 1 requests and eight months for tier 2 submissions, followed by a 45-day comment period, two more months to assess the comments and another eight weeks to draft an order.

Collier also described a third option for submitting OMORs for marketing a product a different dosage device than currently allowed by a monograph. FDA would have to publish an order and guidance to define the third option fully as "kind of a middle ground of innovation that will be available," he said.

Additionally, as they are with investigational new drug proposals and NDAs, firms are encouraged to meet with Center for Drug Evaluation and Research staff at least 120 days before making OMORs.

"More or less like a pre-IND or a pre-NDA meeting where you can talk real specifics about what's going into the request," Collier said.

While this new approach is intended to address industry calls for monograph program reform, the bulk of the user fee funds are expected to come from facility registration fees rather than tier 1 and 2 OMORs.

From the editors of The Tan Sheet.
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All Set For EU Approval: First Biosimilar Humalog And Three More Rituximabs From Celltrion

IAN SCHOFIELD ian.schofield@informa.com
MAUREEN KENNY maureen.kenny@informa.com

Four biosimilars – including the first biosimilar competition to Lilly's diabetes drug Humalog – are among the products the European Medicines Agency's main scientific committee, the CHMP, has just recommended for EU-wide approval. The products are Sanofi's insulin lispro, a biosimilar of Lilly's Humalog, and three more versions of Roche's MabThera (rituximab) from Celltrion, which received EU approval for the first biosimilar rituximab, Truxima, in February.

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Insulin lispro Sanofi (SAR342434) was recommended for use in adults and children with type 1 or 2 diabetes, including those whose condition has just been diagnosed. "This positive opinion is the company's first major regulatory milestone for a biosimilar diabetes treatment," Sanofi said.

The CHMP recommended the products for approval at its latest monthly meeting, which took place this week. CHMP recommendations go to the European Commission for a final decision on marketing authorization. The Commission usually follows CHMP recommendations, and decisions are usually taken within two to three months. Several other products, including an advanced therapy product *(Also see "Decade-Old Advanced Therapy Set For EU Approval" - Pink Sheet, 19 May, 2017.)*, also secured positive opinions. Three products – from Helsinn, AB Science and XBiotech – received negative opinions and one application for an initial marketing authorization – from Sunesis – has been withdrawn.

Assuming it's now approved by the European Commission, Sanofi's product will also provide the first biosimilar competition for Humalog, which reached the market as the first insulin analog more than 20 years ago, having been granted an EU marketing authorization in April 1996.

"Insulin lispro is an important and widely-used treatment for people with diabetes who require rapid control of their blood sugar at mealtime," said Peter Guenter, Sanofi's executive vice-president and general manager, diabetes & cardiovascular. "By broadening our portfolio of quality insulin options, we acknowledge our commitment to expand the affordability and sustainability of insulin treatments."

Sanofi will be looking to the biosimilar to help the company address its diabetes portfolio problems. Sales of its own insulin product, Lantus (insulin glargine), are declining due to competition from the likes of Lilly/Boehringer Ingelheim's biosimilar version, Abasaglar, which received an EU marketing authorization in September 2014.

The EMA accepted Sanofi's filing in September 2016 following the completion of two multicenter Phase III clinical trials, SORELLA 1 and SORELLA 2. *(Also see "Sanofi's Franchise Defense Sees Biosimilar Insulin Lispro Under EU Review" - Scrip, 14 Nov, 2016.)* Sanofi has also developed Toujeo, a longer-acting version of Lantus approved in the EU in April 2015, in an effort to extend its diabetes franchise.

Other companies are working on biosimilar versions of insulin lispro, including Biocon of India (which is also developing biosimilar insulin glargine and insulin aspart (Novo Nordisk's NovoLog/NovoRapid)).

Meanwhile, in an apparent attempt to offset biosimilar competition to Humalog, Lilly had been developing a newer version of the product, BioChaperone Lispro, with the French company Adocia. The product was being tested against Humalog with what looked like promising results, but in January this year Lilly pulled out of the 2014 agreement. Adocia said it would continue developing the drug.

RITUXIMABS FROM CELLTRION

The three rituximab approvals – Celltrion's Blitzima, Tuxella and Ritemvia – will serve to increase the competition for MabThera. They are all indicated for non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), apart from Ritemvia which lacks the CLL indication.

If the products are approved, Celltrion will have a total of four biosimilar rituximabs under its belt. It gained EU approval for the first one, Truxima, in February this year for a slightly different range of indications: NHL, CLL, GPA and severe rheumatoid arthritis.

Sandoz is also in the running, having gained positive opinions for two rituximab products, Rixathon and Riximyo, at the CHMP's meeting last month. They both have the same indications (NHL, RA, GPA and MPA), although Rixathon also has CLL – a difference the company explained as relating to "potential patent implications" in some EU countries. *(Also see "EU Approval Recommendations: Strong Showing From Orphans & Biosimilars" - Pink Sheet, 24 Apr, 2017.)*

NEGATIVE OPINIONS AND WITHDRAWAL

The products that received negative opinions were:

- **Helsinn Group**'s *Adlumiz*(anamorelin hydrochloride), which was expected to be used to treat anorexia, cachexia or unintended weight loss in patients with non-small cell lung cancer.
- **AB Science**'s *Masipro* (masitinib), which was intended to be used to treat systemic mastocytosis..
- **XBiotech Inc.**'s human IgG1 monoclonal antibody specific for human interleukin-1 alpha, which was intended to treat debilitating symptoms of advanced colorectal cancer.

Sunesis Pharmaceuticals Inc. has withdrawn its application for *Qinprezo* (vosaroxin), which was intended to be used in combination with the cancer medicine cytarabine for the treatment of acute myeloid leukaemia.

The companies that received negative opinions have 15 days in which to decide whether to request a re-examination of the opinion. XBiotech and AB Science plan to do so; it seems Helsinn will not.

XBiotech said in a filing with the US Securities and Exchange Commission: "The Company plans to promptly notify the EMA of its request for a re-examination and will have 60 days to submit its grounds for appeal. The Company firmly believes it has a strong position for re-examination."

AB Science issued a three-page statement explaining its grounds for requesting a re-examination.

Helsinn told the *Pink Sheet*: "Helsinn is in discussion with the European Medicines Agency on next steps for an additional Phase 3 trial and will provide an update when possible."

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Indian Insurer Urges Hospitals To Prescribe Generics As 'No Name' Campaign Gathers Pace

PENELOPE MACRAE pinkeditor@informa.com

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One of India's leading insurers, Max Bupa Health Insurance, has told hospitals their doctors should prescribe non-proprietary generic medicines rather than branded ones wherever possible.

The New Delhi-based insurer's call follows Prime Minister Narendra Modi's announcement last month that the government plans to introduce a "legal framework" obliging doctors to prescribe no-name generics to cut treatment costs.

Citing Modi's drug cost-cutting drive, a Max Bupa spokesperson told *Pink Sheet* the insurer was interested in making treatment "more affordable" for patients in India, where just 288 million people - or around 20% of the 1.25 billion population - were

covered by some form of health insurance in 2015, according to the insurance regulator.

But the insurer's spokesperson, who declined to be named, emphasized "nothing has been decided" and that "this is more of a conversation" and a "reminder of something the government is promoting."

Max Bupa said in a letter to hospitals they should "segregate the drugs with generic names from the branded names in the invoice… [and] a clear justification for not using generic drugs under certain circumstances must be written," according to *The Economic Times* newspaper.

Drugs make up around 70% of healthcare bills and treatment costs push at least 55 million people into poverty annually, official figures estimate. Due to a struggling public healthcare sector, which lacks infrastructure, equipment and staff, the private sector provides nearly 80% of outpatient care and 60% of in-patient care.

INSURER WILL 'HONOR AND PAY ALL CLAIMS'

A statement by the insurer, a joint venture between publicly listed holding company Max India Ltd and UK-based healthcare services firm Bupa, sent later to *Pink Sheet* said the company would continue to "honor and pay all claims as per the policy terms and conditions."

Modi has been sounding more populist as he gears up for national elections due in two years and declared he is braving the "wrath of a very powerful [pharmaceutical manufacturing] lobby." The government has widened the number of essential drugs under price controls, capped prices of coronary stents and is looking at including other medical devices in the crackdown and created a basic insurance scheme to help poor people cope with "catastrophic health events."

Still, the government has kept public healthcare spending as a percentage of GDP at around 1%, one of the lowest rates globally, despite exploding rates of diabetes, heart disease and cancer.

The call for doctors to prescribe non-proprietary generics has sparked intense debate among the medical fraternity, with many objecting to any step curbing doctors' prescription choices. They say it could hurt patient safety in India where mechanisms to police quality at the thousands of manufacturing sites and hundreds of thousands of pharmacies are widely deemed, even by regulators, to be inadequate.

In the absence of stringent controls, doctors have come to trust some, usually bigger, companies for quality. Also, critics say writing only generic names on prescriptions would hand too much power to pharmacists who might dispense drugs offering the best margins, some of which could be of dubious quality.

DOCTORS, NOT INSURERS, HAVE RIGHT TO PRESCRIBE: HOSPITAL ASSOCIATION

The right to prescribe the generic drugs or brand "rests with the registered medical practitioner and not with chemists or any insurance company," said Dr. R.V. Asokan, chairman of The Indian Medical Association Hospital Board of India, which represents hospital chains in India.

Still, while the Medical Council of India (MCI) recently reiterated longstanding guidelines that doctors should prescribe no-name generics, they "do not make it mandatory," Asokan said, *The Economic Times* reported. Also, an "insurance company compelling hospitals to write generic medicines…[would be] unwarranted and unethical," he said.

In developed economies such as the US and the EU, doctors routinely prescribe non-proprietary low-cost generic drugs. But branded generics and originator or off-patent brands dwarf prescriptions of pure generics in India and this pushes up care bills for patients.

"Clearly, any move to prescribe non-proprietary generics would bring down costs for insurers and patients and would be welcome. It's a good thing as long as the government makes sure the care element is looked after - but the drugs have to be the same quality," Nilaya Varma, a KPMG India partner and chief healthcare operating officer, told *Pink Sheet*.

Complaints abound from healthcare activists and patients that doctors at private hospitals and in private practice often prescribe expensive branded drugs because of revenue targets and commissions. In India, branded generics can be 10 times costlier than pure generic offerings, according to Drug Controller General G.N. Singh, although sometimes the gap is much smaller.

"Ironically, India, which has a huge generics industry in its backyard that it supplies to the world, lacks the mechanism to offer generic drugs to its own people," public health lawyer Leena Menghaney told *Pink Sheet*.

QUALITY CONCERNS

Drugs exported by India also undergo stringent quality tests, though foreign regulators have found quality-control lapses involving some of India's biggest domestic manufacturers. But regulation of drugs sold domestically is far patchier and in absence of strict quality controls, doctors have come to trust some, usually bigger, companies for quality more than others.

A recent government study found 10% of all drugs from "government sources" - ie, government dispensaries - in India were "not of standard quality" or NSQ. At the retail level, NSQ samples totaled 3% and some that flunked were from well-known companies.

Health Minister J.P. Nadda told reporters the government is looking at ways to ensure across-the-board drug quality and address other concerns voiced by medical practitioners. "We're considering legal routes to make generics mandatory, we're looking at amendments to laws," he added.

A health department official said making it obligatory for doctors to prescribe non-proprietary generics could involve a change to the 1956 Indian Medical Council Act.

"It's a good idea [prescribing by generic names only], but we're not ready for it yet. That doesn't mean we shouldn't start working toward it," said Dr. Indranil Mukhopadhyay, research scientist at the Public Health Foundation of India, a public-private initiative.

From the editors of PharmAsia News. Published online May 24, 2017

Tweaked 'New Drugs' Flouted Price Approval Norms In India

ANJU GHANGURDE anju.ghangurde@informa.com

India's National Pharmaceutical Pricing Authority (NPPA) has fired a fresh salvo, pulling up over 50 companies, both local and foreign, for allegedly introducing 201 "new drugs" on the market without applying for requisite price approvals.

NPPA said that some firms launched formulations by "altering" a scheduled formulation with strengths or dosages other than as specified in India's Drug Prices Control Order (DPCO) 2013 and/or in combination with other non-scheduled medicines "without even applying for price approval from NPPA as required." Such tweaked formulations are categorized as "new drugs" as defined under para 2 (u) of the DPCO 2013.

Scheduled drugs are those that fall in India's national list of essential medicines (NLEM) and attract price control, while non-scheduled medicines typically don't figure in the NLEM. Prices of these non-scheduled drugs are not capped, but the regulator can monitor their prices.

But the seeming sting in the tail came when an NPPA "office memorandum" dated May 17 said that it is unclear whether the concerned 201 medicines have been cleared by India's Central Drugs Standard Control Organization (CDSCO) or "whether these are rational or irrational drugs," as many of these are fixed-dose combination drugs." The Indian government took action against fixed-dose combination products when there appears to be no rational medical reason for making them in combination. *(Also see "India To Weed Out Over 300 Fixed-Dose Combos; Next Round In Court" - Scrip, 14 Mar, 2016.)* The Delhi High Court had earlier struck down a controversial order aimed at weeding out over 300 irrational combination products, though the government has since moved the Supreme Court and the case is ongoing.

In the May 17 memorandum, NPPA asked that concerned firms furnish by June 15 batch-wise production and sales details, and the MRP [maximum retail price] of the drugs in question since the launch of production, along with reasons for non-compliance with norms.

NPPA asked firms to furnish by June 15 batch-wise production and sales details, and maximum retail price of the drugs in question, along with reasons for noncompliance.

The DPCO stipulates that manufacturers of scheduled formulations who fail to apply for prior price approval of a 'new drug' are liable to deposit the overcharged amount for these drugs with interest from the date of launch, in addition to a penalty.

SANOFI - COMPLIANT?

The latest NPPA order names leading foreign and Indian firms including Sanofi India Ltd., Abbott Healthcare Pvt Ltd., **GlaxoSmithKline Pharmaceuticals Ltd.**, Novartis India, **Lupin Ltd.**, **Dr. Reddy's Laboratories Ltd.** and **Alembic Pharmaceuticals Ltd.**, among others, specifying their respective brands allegedly launched without the requisite pricing approvals. Launch dates and the maximum retail price of the products too have been specified by the price regulator.

Sanofi, however, told the *Pink Sheet* that it is "fully compliant" with the provision of the DPCO "in all respects." Sanofi's *Amaryl MV* (voglibose/metformin/glimepiride) is on the NPPA list of products.

"The NPPA has stated that on receipt of satisfactory representations, names of the companies will be dropped from the list. We are in the process of sending our response to NPPA and are confident that after considering the same, NPPA will remove our products from the list of suspected non-compliance," Sanofi said.

The French multinational also maintained that publishing a list of non-compliant companies merely on the basis of "suspicion," without seeking the manufacturer's clarification, causes public confusion and "unnecessarily damages the painstakingly built trust-quotient and reputation of the manufacturers."

"Notices should be served to the concerned manufacturers for a clarification within a stipulated time-period prior to publishing the names in public domain," it said in response to specific queries from the Pink Sheet. Last month the NPPA had put out a list of "suspicious cases" of non-compliance of ceiling prices covering 613 such cases.

OTHER RESPONSES

Meanwhile, others like GlaxoSmithKline Asia Pvt. Ltd. told the Pink Sheet that its brand, *Crocin Cold and Flu Max*, pulled up by the regulator, "doesn't fall under the purview of price approval."

"However, we are going through the office memorandum issued by the NPPA and will respond appropriately. GlaxoSmithKline Asia Pvt. Ltd. is a responsible company, complying with the law of the land, driven by values and committed to bringing the best for consumers," it added.

Similar positions were echoed by some other firms. Novartis maintained that it is committed to high standards of ethical business conduct and regulatory compliance in all aspects of its work. "In the notification issued by NPPA, two Novartis products have been featured. We will send our response along with documented evidence to NPPA shortly."

Abbott said that it is in the process of

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reviewing the show-cause notice and will provide "necessary details" to the NPPA. Certain cefixime and also ceftriaxone combination brands of Abbott feature on the latest list of the NPPA.

VERACITY OF DATA

While several other companies on the NPPA's latest list of those flouting pricing rules could not immediately be reached, industry experts suggest that it's unlikely that large Indian and foreign companies would indulge in such practices.

The Indian Pharmaceutical Alliance (IPA), which represents leading domestic firms, said that it has, nevertheless, requested its members to confirm the "veracity of the data" released by the NPPA.

"Our experience of data used by the NPPA is a mixed one. Hence, we will wait until companies named by the NPPA respond," Dilip Shah, IPA' s secretary general, told the Pink Sheet.

On whether some of these fixed-dose combinations on the list included those apparently deemed irrational by the 'Kokate Committee' and are part of the ongoing legal tussle, with the NPPA's notice now adding fuel to the fire, Shah said that he doubts if any large company will launch an FDC that is already deemed irrational.

"These are probably 'existing' products in terms of Para 2(u) of the DPCO 2013. If so, this public notice [by the NPPA] is irrelevant as the manufacturers were not obliged to seek a price approval," Shah underscored.

The government had, in 2014, constituted a committee under the chairmanship of Dr. C.K. Kokate, vice chancellor of the KLE University, to look into the issue of the safety and efficacy of certain FDCs.

Part of the reason for irrational FDCs on the Indian market, some experts say, can also be attributed to India's dual regulatory control, i.e. state as well as the center. Several of the FDCs were approved by the respective state FDAs in the past, but the Central Drugs Standard Control Organization has since reiterated that such new drug manufacturing approvals need to be first cleared by the Drugs Controller General of India.

From the editors of PharmAsia News. Published online May 19, 2017

EMA Consults On Managing Serious Breaches Under EU Clinical Trials Regulation

VIBHA SHARMA vibha.sharma@informa.com

The European Medicines Agency is inviting feedback on a draft guideline that offers practical advice for sponsors on notifying serious breaches under the upcoming EU Clinical Trials Regulation.

The draft guideline explains what should or should not be classified as a serious breach and what must be reported. It also outlines possible actions that the EU member states may take in response to notifications of serious breaches.

All serious breaches – ie, anything that may affect to a significant degree the safety and rights of a subject, and/or the reliability and robustness of the data generated in a clinical trial – should be notified within seven working days of the sponsor becoming aware of the breach, the draft guidance says.

In cases where a sponsor has "reasonable grounds" to believe that a serious breach may have occurred, the guideline states that the sponsor should not wait to obtain all of the details of the breach. In such cases, the EMA expects the sponsor to first report the breach within the seven-day deadline, and investigate and take action simultaneously or after notification.

The guideline proposes different requirements for notifying serious breaches based on whether or not the incident takes place in the EU/European Economic Area. For example, it states that if a serious breach occurs outside the EU/EEA while an application to authorize the trial is still being evaluated in an EU/EEA territory, and the breach can affect the accuracy or robustness of data submitted in the dossier, then the sponsor should withdraw the application and correct the aspects or data impacted, as applicable.

Serious breaches occurring exclusively outside the EU/EEA that may affect the integrity of data of a trial already authorized or being conducted in the EU/EEA territory should be notified to the concerned member state within the seven-day deadline., the draft document says.

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If there is are serious breaches of the protocol of an EU/EEA authorized clinical trial occurring exclusively outside the EU/EEA that are likely to affect the safety and the rights of a subject and/or the benefit-risk balance of trial already authorized or being conducted in the EU/EEA territory, then it should be notified to the concerned member state within seven working days, according to the draft document. In addition, the sponsor would have to report the incident as an unexpected event (under Article 53) or as an urgent safety measure (under Article 54), as applicable.

Besides offering guidance on general factors that sponsors should consider when reporting serious breaches and the responsibilities of various parties involved in the notification process, the document contains a non-exhaustive list of what may or may not qualify as a serious breach.

Stakeholders have until Aug. 22, 2017 to comment on the draft guideline.

From the editors of Scrip Regulatory Affairs. Published online May 24, 2017

Biopharma Patent Disputes: Upheaval Likely As US Supreme Court Limits Litigation Venue

BRENDA SANDBURG brenda.sandburg@informa.com

The US Supreme Court's ruling that patent infringement lawsuits may be brought against a domestic corporation only where the company is incorporated could have a detrimental impact on biopharma patent owners by preventing the consolidation of ANDA suits and pulling them into more venue disputes.

In TC Heartland LLC v. Kraft Foods Group Brands LLC, the court concluded in a May 22 opinion that congressional amendments to the general venue statute did not alter its 1957 decision in Fourco Glass Co. v. Transmirra Products Corp., which held that where a defendant "resides" under the patent venue statute is limited to where the company is incorporated.

"Going forward, venue will be governed by 30-year old precedent that predates the Internet, predates biotechnology, predates e-commerce," Hans Sauer, Biotechnology Innovation Organization's deputy general counsel for intellectual property, said. "To the extent some may be celebrating this case as putting an end to venue shopping, that is not a foregone conclusion. It is more likely to lead to something new in litigation."

For example, Sauer said it will be very attractive for someone accused of patent infringement to first litigate whether the complaint was filed in the right place, which will delay litigation.

Melissa Brand, BIO associate counsel and director of IP policy, noted that ANDA litigation will be particularly affected by the ruling. For a long time, cases against ANDA filers have been brought before a single district court so there are not competing orders on issues such as claim construction. Now, she said, these cases will probably be handled in multiple courts across the country.

Brand said the decision also could possibly lead to patent owners bringing creative claims to get around the patent venue statute, such as trade secret theft or tortious interference claims. In addition, there could be more suits filed against end users.

The Pharmaceutical Research and Manufacturers of America said it is very disappointed by the court's decision. It also cited the impact the ruling will have on Hatch-Waxman ANDA litigation.

In the past, when the same patent was challenged by multiple generic companies, "innovator companies have had the ability to bring at least some resulting lawsuits in the same court. The result of today's decision could lead to litigation over the same biopharmaceutical patent in more courts, which is inefficient, could enable and encourage inconsistent rulings, and would be an additional burden on the innovative companies' time and resources," the association said in a statement.

PATENT VENUE VS. GENERAL VENUE

The current version of the general venue statute adopted by Congress in 2011 states that for all venue purposes, a corporation "shall reside, if a defendant, in any judicial district in which such defendant is subject to the court's personal jurisdiction with respect to the civil action in question."

"The issue in this case is whether that definition supplants the definition announced in *Fourco* and allows a plaintiff to bring a patent infringement lawsuit against a corporation in any district in which the corporation is subject to personal jurisdiction," the Supreme Court stated. "We conclude that the amendments to [the general venue statute] did not modify the meaning of [the patent venue statute] as interpreted by Fourco. We therefore hold that a domestic corporation 'resides' only in the State of incorporation for purposes of the patent venue statute."

Justice Clarence Thomas wrote the 8-0 opinion for the court. Justice Neil Gorsuch took no part in the decision.

TC Heartland challenged Kraft's filing of an infringement suit in the District of Delaware alleging TC Heartland's liquid water enhancer products infringe three of its patents. A district court denied Heartland's motion to transfer the complaint on the grounds that it did not reside in that district. The US Court of Appeals for the Federal Circuit affirmed, finding that Congress' 1988 amendments to the federal code governing civil actions brought in district courts made the definition of corporate residence applicable to patent cases.

PhRMA, BIO and the Association of University Technology Managers, and **Genentech Inc.** filed amicus briefs in support of Kraft Foods asking the court to affirm the Federal Circuit's decision and not limit patent litigation venue. The Generic Pharmaceutical Association, now called the Association for Accessible Medicines, submitted a brief in support of Heartland arguing that the Federal Circuit's ruling effectively subjected generic defendants to suit in any district court in the nation. *(Also see "Biopharma Asks US Supreme Court Not To Limit Patent Litigation Venue" - Pink Sheet, 26 Mar, 2017.)*

COURT TO DECIDE STATE COURT JURISDICTION IN PLAVIX CASE

The question of which court should handle a dispute has been hotly contested in recent pharma litigation. The Supreme Court declined to take up **Mylan NV**'s petition seeking review of a court's personal jurisdiction, i.e., whether a court has authority over parties. In that case, Mylan v. **Acorda Therapeutics Inc.**, Mylan sought

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to dismiss infringement suits brought by Acorda and **AstraZeneca PLC** in the District of Delaware on the grounds that the state of Delaware, and therefore the district court, could not exercise personal jurisdiction over Mylan since the company had no connection to it.

The Federal Circuit ruled that Mylan's filing of an ANDA is sufficient grounds for an infringement suit to be brought in Delaware since Mylan would be marketing its generics in the state once they were approved.

In April, the Supreme Court heard oral arguments in another jurisdictional dispute involving whether a state court has jurisdiction over a defendant when there is no relationship between the defendant's state contacts and the plaintiff's suit. In that case, **Bristol-Myers Squibb Co.** v. Superior Court of California for the County of San Francisco, Bristol-Myers is challenging the inclusion of non-California residents in a product liability suit alleging BMS and its distributor **McKesson Corp.** misrepresented the safety of *Plavix* (clopidogrel).

The justices questioned whether it is fair for a court to have jurisdiction over cases involving out-of-state plaintiffs and out-of-state defendants. *(Also see "Paxil's Day In Supreme Court: Is California Playing Fair On Product Liability?" - Pink Sheet, 25 Apr, 2017.)*

INTER PARTES REVIEW GETS MORE SUPREME COURT SCRUTINY

In another case that could have ramifications for the life sciences industry, the Supreme Court agreed on May 22 to hear a challenge to the US Patent and Trademark Office's Patent Trial and Appeal Board (PTAB) handling of inter partes review (IPR) cases.

In SAS Institute Inc. v. Lee, SAS asks the court to decide if the Board's final written decision in an IPR proceeding may address the patentability of only some of the patent claims challenged by the petitioner. The Federal Circuit rejected SAS' argument that under the America Invents Act, the Board must address all claims raised in an IPR petition in its final decision.

The Federal Circuit cited its February 2016 decision in Synopsys Inc. v. Mentor Graphics Corp. in which it held that the Board was authorized to adopt a partial final written decision regimen. Federal Circuit Judge Pauline Newman dissented in both the Synopsys and SAS decisions.

In its certiorari petition, SAS quotes Newman, saying that the Federal Circuit's reading of the America Invents Act "leaves the unselected claims dangling, lacking both finality and estoppel, preventing the expedience and economy and efficiency that motivated the America Invents Act."

Sauer said BIO will have to consider the case to determine its position on the outcome it would like to see. "On the one hand, if PTAB has to litigate every ground for a patent challenge in a petition, it will increase the workload of administrative judges and increase the complexity and cost for both parties," he said. "On the other hand, there is something to be said for business certainty. It would not be good if there are 50 reasons given why a patent is invalid and PTAB decides five and lets the other 45 hang out there."

This will be the second case the Supreme Court has taken up involving questions over IPR proceedings. Last year, in Cuozzo Speed Technologies v. Lee, the court upheld PTAB's use of the "broadest reasonable interpretation" standard for determining the meaning of patent claim terms. *(Also see "Supreme Court Upholds IPR Standard Making Patent Invalidation Easier; Will Congress Reverse?" - Pink Sheet, 20 Jun, 2016.)*

Published online May 22, 2017

FDA's NDA And BLA Approvals: Kevzara

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 Biologics				
Sanofi/ Regeneron	*Kevzara* (sarilumab)	Interleukin-6 receptor for treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs.		5/22/2017

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

Brand Exclusivity 'Gaming' To Be Addressed At US FDA Meeting

MICHAEL CIPRIANO michael.cipriano@informa.com

Newly sworn in FDA Commissioner Scott Gottlieb is beginning to put his stamp on the agency in an effort to foster more robust competition in the generic marketplace, as the agency will hold a public meeting to solicit ideas on how to stop companies from "gaming" the regulatory system and having longer exclusivity periods than Congress intended for their products.

Gottlieb said at a May 25 House Appropriations Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies budget hearing that the agency will convene consumer representatives and the broader public to gather feedback on why the issue might be happening.

"We need to make sure that there is a capacity for market entry for competition after patents have expired, patent periods that Congress intended," Gottlieb said in his first congressional testimony as commissioner. "I don't want to be in a position of playing Whac-A-Mole with companies. What I want are clear rules and bright lines in place that prevent these kinds of abuses."

FDA will be formally announcing the meeting in the near future, Gottlieb said, adding that FDA is working on a "drug competition action plan," which will be revealed soon.

The announcement of the meeting nevertheless was one of the several aspects the commissioner mentioned at the hearing giving a wider peek into his broader strategy of creating a competitive generic drug market, which has consistently been one of his stated top priorities as head of the agency.

ADDRESSING REMS ABUSE

Gottlieb also made noted that FDA will be working to curb abuses of Risk Evaluation and Mitigation Strategies (REMS) by innovators.

The issue has garnered significant attention from Democrats during recent FDA hearings, although Republicans have mostly shied away from the issue. *(Also see "FDA User Fee Hearing Hijacked By US Health Care Reform Arguments" - Pink Sheet, 21 Mar, 2017.)* Center for Drug Evaluation and Research (CDER) Director Janet Woodcock has also said that REMS obstruction has been a problem in fostering generic competition, as generic sponsors are not always able to get samples of the product from the brand drugmaker. *(Also see "REMS Reform Seems Distant Goal For Generics After Limited Support At US House Hearing" - Pink Sheet, 2 Mar, 2017.)*

> "I don't want to be in a position of playing Whac-A-Mole with companies. What I want are clear rules and bright lines in place that prevent these kinds of abuses." – Scott Gottlieb

Gottlieb said FDA is taking steps to address the issue, including looking at how the agency can "streamline" the process it uses in determining whether to waive the requirement that a generic drug applicant and a brand company share a single system for ensuring safe use.

"We are asking whether FDA can waive this requirement more readily than we have in the past in situations where sponsors cannot reach an agreement after a reasonable period of time on implementation of a shared system," Gottlieb said.

Allowing unshared REMS won't address generic concerns about access to samples – which industry feels needs to be resolved through legislation – uncoupling the REMS could smooth approval of some generics.

DIRECTORY OF UNCOMPETITIVE PRODUCTS

In his opening remarks, Gottlieb put forward a new idea, announcing FDA will publish and regularly update a list of off-patent drugs for which there is no generic competition.

"We believe greater transparency in these circumstances can help entice competitors into the market," Gottlieb said.

"We will consider whether we can provide further transparency measures by disclosing additional information to help generic manufacturers target drugs with little or no market competition."

Robert Califf, Gottlieb's predecessor as head of FDA, touted the idea on Twitter as "a great move," adding that certain legal fixes need to be made to help facilitate generic competition.

Gottlieb also reiterated his priority of improving the processes that allow for generics of complex drugs to be approved. He noted that this particular area of generics is one where products frequently end up with longer exclusivity periods because of the difficulties in developing the generic competitors, adding that "there are things FDA can do from both a policy and scientific standpoint to facilitate to market more generic competition to complex drugs."

During his confirmation hearing before the Senate Committee on Health, Education, Labor and Pensions, Gottlieb stressed that FDA needs to develop better scientific principles for assuring substantial equivalence of generics when traditional measures of bioequivalence may be insufficient.

While Gottlieb's moves to encourage generics put him squarely in the middle of one hot-button political issue, drug pricing, his testimony before the House Appropriations Subcommittee elided another one that could have been seen as even more relevant given the venue: the commissioner barely talked about the Trump administration's budget proposal.

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Gottlieb Distances Himself From Trump's User-Fee Heavy Budget

MICHAEL CIPRIANO michael.cipriano@informa.com

After several lawmakers had declared the Trump administration's budget proposal dead on arrival, US FDA Commissioner Scott Gottlieb danced around the subject of user fees in his first congressional testimony has head of the agency.

Speaking before the House Appropriations Subcommittee on Agriculture, Rural Development, Food and Drug Administration and Related Agencies May 25, Gottlieb did not address the major recalibration of user fees proposed in the president's budget. The Trump proposal would cut FDA budgetary authority by 31%, while hiking user fee funding by 68%. *(Also see "FDA Safety Initiatives Could Suffer Under Trump's Budget Proposal" - Pink Sheet, 23 May, 2017.)*

Subcommittee Chairman Rep. Robert Aderholt, R-Ala., and Ranking Member Rep. Sanford Bishop, D-Ga., both put the official kibosh on any notion reopening the user fee reauthorizations.

"I give someone credit for coming up with a very creative proposal," Aderholt said. "But the legislation before Congress reflects agreements that take up to two years to work out."

Bishop noted that the user fee agreements "are very far along in the legislative process," adding that it is "doubtful" that FDA and stakeholders would be able to renegotiate a new agreement in time before the current set of agreements expire.

Rep. Rosa DeLauro, D-Conn., also put it bluntly when she told Gottlieb that the proposal to sharply increase user fee funding is "quite frankly not going to happen."

Gottlieb, however, passed on his many opportunities to defend the president's budget proposal. He instead spent much of his time speaking informing lawmakers of his plans to foster a more competitive marketplace for generic drugs.

The commissioner additionally discussed issues such as the 21st Century Cures Act, which Gottlieb said the agency would use as a guide in evaluating whether the proper regulatory science is in place to help make medical product development more efficient. Lawmakers also questioned Gottlieb on issues such as food safety and tobacco rules, to which Gottlieb often admitted he was still learning about and pledged to follow up at a later time.

US FDA Commissioner Scott Gottlieb

> Gottlieb also announced at the hearing that the hiring freeze had been lifted at FDA that morning.

In a response to DeLauro about food safety, he noted that he "was not involved in the formulation of the budget," and that he would work with the administration and Congress "to make sure the agency has the resources it needs to fulfill its mission."

Although Gottlieb did not offer a direct critique of his boss' proposal, his evasiveness on the user fee agreements, as well as the distancing of himself from the formulation of the budget, suggest that he might be less than enthusiastic about the president's proposal.

HIRING FREEZE LIFTED

Gottlieb also announced at the hearing that the hiring freeze was lifted at FDA Thursday morning. Although FDA was expected to have broad exemptions from the hiring freeze, it was unclear whether all user fee-funded positions would be in the clear. *(Also see "FDA Gets Broad Exemptions From Federal Hiring Freeze In HHS Memo" - Pink Sheet, 9 Feb, 2017.)*

Senate Health, Education, Labor and Pensions Committee Chairman Lamar Alexander, R-Tenn., praised the lifting of the hiring freeze in that it allows the agency to fulfill the hiring provisions set forth in the 21st Century Cures Act.

"We asked the Food and Drug Administration last year to tell us the single most important thing we could do to help move safe drugs and devices more quickly into patients' medicine cabinets and doctors' offices. And they said it was to allow them to hire talented people and pay them more competitively," Alexander said in a statement.

Published online May 25, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Hospira's (Pfizer) proposed biosimilar to Amgen Inc.'s *Epogen*/*Procrit* (epoetin alfa) for all of the indications on the reference biologic's labeling	Oncologic Drugs	May 25
Novo Nordisk's *Victoza* (liraglutide) as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse CV events in adults with type 2 diabetes and high CV risk	Endocrinologic and Metabolic Drugs	June 20
Potential pediatric development plans for Apexigen's APX-005M, PharmaMar USA Inc.'s PMO1183 (lurbinectedin) and Astellas Pharma Global Development's ASP2215 (gilteritinib)	Pediatric Oncology Subcommittee	June 21
Potential pediatric development plans for Dista Products/Eli Lilly's prexasertib and Lilly's olaratumab	Pediatric Oncology Subcommittee	June 22
Safety and efficacy of Dynavax's hepatitis B vaccine	Vaccines and Related Biological Products	July 28

Pink Sheet

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CORPORATE SALES
John Lucas, Elissa Langer

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Christopher Keeling

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Jean Marie Smith

US
Denise Peterson
Nielsen Hobbs
Mary Jo Laffler

Europe
Eleanor Malone
Maureen Kenny

Asia
Ian Haydock

POLICY AND REGULATORY

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Michael Cipriano
Bowman Cox
Joanne Eglovitch
Eileen Francis
Derrick Gingery
Cathy Kelly
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EDITORIAL OFFICE
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