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INSIDE THIS ISSUE

FDA Commissioner Prods Stretched Centers to Streamline Operations

To help the agency cope with a growing list of legislative mandates and limited resources, FDA Commissioner Margaret Hamburg has called on center directors to streamline the way the agency operates.

Hamburg Sept. 6 established a new in-house team of top brass called the Program Alignment Group (PAG). In a memo to the 10-member group of center directors, she asks them to "identify and develop plans to modify agency functions and processes in order to best achieve mission-critical agency objectives." The effort requires more "clarity and transparency" about each office's operational roles with a goal of eliminating duplication, the memo says.

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FDA Posts List of Facilities That Have Yet to Pony Up GDUFA Fees

The FDA Sept. 4 posted a list of manufacturing facilities that have failed to submit their annual facility fee required under the Generic Drug User Fee Act (GDUFA) of 2012. It's the second time in as many weeks that the agency has named names as a means to spur compliance.

In August, the agency published noncompliance letters and company responses from those drugmakers that have failed to fulfill certain pediatric clinical trial requirements.

It's a tactic that seems to work. Just hours after posting the "GDUFA Facility Arrears List" to the user fee section of its website, the FDA posted an updated list naming 43 facilities instead of 44.

Being named to the list has huge implications not only for the facilities themselves, but also drugmakers contracting work out to them. The FDA said it will not receive new ANDAs or prior

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GDUFA Fees, *from Page 1*

approval supplements referencing the facilities until the outstanding fee is paid. The agency will also not process applications submitted by the owner or any affiliates of the listed facilities.

Fixed dosage forms (FDF) or active pharmaceutical ingredients (API) manufactured in facilities that have not paid the fees will also be classified as misbranded by the FDA, making it a violation of federal law to ship the products in interstate commerce or import them into the U.S.

The agency announced the facility fees in January with a due date of March 4 (*Generic Line*, Jan. 30). In August, the agency announced fiscal 2014 GDUFA fees, including the new facility fees due Oct. 1, 2013 (*Generic Line*, Aug. 14).

The fiscal 2014 facility fees are:

- U.S. FDF facilities: $220,152;
- Non-U.S. FDF facilities: $235,152;
- U.S. API manufacturing facilities: $34,515; and
- Non-U.S. API facilities: $49,515.

GDUFA requires the FDA to charge facilities located outside the U.S. at least $15,000 more than U.S. facilities, but no more than an additional $30,000 due to foreign-facility inspection costs.

Invoices will not be issued to facilities in arrears except in rare circumstances (*Generic Line*, Aug. 29, 2012).

The arrears list can be viewed at www.fdanews.com/ext/files/09-04-13-GDUFA-Arrears-List.pdf. — Melissa Winn

Blockbuster Biologic Remicade Threatened By Second Biosimilar

A Phase III study comparing the autoimmune therapy Remicade to the biosimilar BOW-015 has shown the two drugs to be similar in efficacy and safety for treating severe rheumatoid arthritis after 16 weeks.

According to EPIRUS Biopharmaceuticals, the pivotal study recruited 189 patients. Of those, 127 patients were randomized to the company's lead biosimilar, BOW-015, arm and 62 to the Remicade (infliximab) arm. After 16 weeks, researchers found those receiving the biosimilar had an ACRO20 response rate of 89.8 percent compared with 86.4 percent for those on Remicade.

"The Phase 3 data announced [Aug. 29] is an important milestone for us and underscores the technical competency of the EPIRUS team," said CEO Amit Munshi. "We plan to submit regulatory filings in targeted emerging markets over the next 12 months."

After week 22 of the study, patients on the Remicade arm were moved over to the BOW-015 arm. The company says it will continue to observe all of the patients through week 52 to determine whether the biosimilar meets the study's secondary endpoint of long-term efficacy and safety.

BOW-015 isn't the first biosimilar to threaten Remicade. Recently, Hospira got a nod from the European Medicines Agency's Committee for Medicinal Products for Human Use to market its biosimilar Inflectra. — Ferdous Al-Faruque

New Paragraph IV Patent Certifications (As of Sept. 3, 2013)

DRUG NAME	DOSAGE FORM	STRENGTH	RLD (Sponsor)	DATE OF SUBMISSION
Buprenorphine Hydrochloride and Naloxone Hydrochloride	Sublingual film	2 mg/0.5 mg and 8 mg/2 mg	Suboxone	10/15/2012
Oxcarbazepine	Extended-release tablets	150 mg and 300 mg	Oxtellar XR	4/12/2013
Prednisone	Delayed-release tablets	1 mg, 2 mg, and 5 mg	Rayos	11/26/2012

Generic drugmakers file ANDAs with Paragraph IV certifications on drugs where patent coverage still exists and they intend to market generics before the patent expires if approved.

California Assembly, Senate Pass Controversial Biosimilar Bill

The California State Assembly voted 58-4 Aug. 26 to pass controversial legislation opposed by the generics industry forbidding a pharmacist from substituting a biosimilar drug for a brand-name biologic if a physician says not to. The Senate passed the bill Sept. 4.

The bill now awaits Gov. Jerry Brown's signature. There is no indication as to whether he will sign or veto it. He has until Oct. 13 to sign the bill into law, a spokesperson for the governor told *Generic Line*.

The bill also requires pharmacists to notify the doctor and sometimes the patient when a substitution is made.

California joins a growing list of states advancing such legislation, which GPhA President and CEO Ralph Neas calls "additional layers of red-tape and roadblocks" designed to restrict access to less-expensive drugs. The bills are heavily promoted by Genentech and California-based Amgen.

The California bill, SB 598, "imposes unnecessary physician notification requirements on pharmacists that could potentially reduce the number of prescriptions substituted with biosimilars," Danny Brown, a lobbyist for the California Public Employees' Retirement System, wrote in an Aug. 21 letter to the measure's sponsor, state Sen. Jerry Hill (D-San Mateo).

The California State Board of Pharmacy calls the bill "premature," since the FDA has yet to approve a biosimilar or even to pass guidance on the issue (*Generic Line*, Sept. 26, 2012).

The appropriate time to make changes to California law would coincide with the FDA's approval of a biosimilar, Virginia Herold, the board's executive officer, said in a letter to Hill. For instance, she notes, the bill would require the pharmacy board to post a link to a list of biosimilar drugs approved by the federal government as interchangeable, but no such list currently exists.

The final version of the bill requires pharmacists to notify a doctor within five business days to state whether a prescription was filled with the brand biologic or an interchangeable biosimilar drug. The physician notification requirement applies to prescriptions filled before Jan. 1, 2017.

The three-year sunset on the notification clause was added in the Senate Business, Professions, and Economic Development Committee, with the expectation that California's looming e-Pedigree track-and-trace system for pharmaceuticals will offer more accountability for biosimilars by then, according to an analysis of the bill prepared for lower-house lawmakers.

Similar legislation passed by Oregon, Utah and Virginia also contains a sunset clause, which most experts believe will render the restrictive sections moot before biosimilars come to market (*Generic Line*, March 27).

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Novartis Wants FDA Accusation Of 'Misuse' Stricken From Public Record

Novartis is asking the FDA to retract from public record accusations it misused the citizen petition process to stall approval of generic versions of Reclast, saying the agency's statement is contrary to evidence and "could chill" other drugmakers from submitting concerns in similar circumstances in the future.

In an Aug. 1 response letter, the FDA asserts that a citizen petition filed by Novartis March 1 — one day before tentatively approved ANDAs for Reclast (zoledronic acid) could have been approved — is an "egregious misuse of the FDA citizen petition process for what appears to be the purpose of delaying generic competition."

But Novartis' petition asking the FDA to deny approval of certain ANDAs for Reclast was not filed until after the company learned at a Feb. 26 court hearing that the drugmakers planned to seek approval of their generic versions with a "carved-out Paget's-only label," Novartis is now arguing in its defense. Reclast is approved for both Paget's disease and osteoporosis.

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FDA Makes Permanent Plaisier's Role As Office of Regulatory Affairs Chief

Melinda Plaisier, chosen last year to head the FDA's Office of Regulatory Affairs (ORA) in an acting role, is now officially the office's chief, effective immediately, the agency said Sept. 5.

As associate commissioner for regulatory affairs, Plaisier helps implement expanded FDA authorities granted under FDASIA, FDA Commissioner Margaret Hamburg said (*Generic Line*, July 17). Plaisier has been filling the role in an acting capacity since Oct. 1, 2012, following a restructuring of ORA designed to help the office respond to globalization.

Plaisier joined the agency in 1995, after serving as a congressional staffer for more than a decade. She spent more than 13 years in the Office of the Commissioner where she served as the associate commissioner for legislation and the associate commissioner for international programs. Before assuming her most recent, acting regulatory affairs role, Plaisier served as the regional food and drug director for ORA's central region for several years. — Melissa Winn

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PAG, *from Page 1*

"More specifically, we need to transition to distinct commodity-based and vertically-integrated regulatory programs with well-defined leads, coherent policy and strategy development, well-designed and coordinated implementation, and a de-layered management structure." Hamburg asked the group to begin developing a core set of operational changes covering areas such as:

- Specializing FDA inspection and compliance functions to help the agency meet the demands of the FDA Safety and Innovation Act and its new user fee programs;
- Staff training enhancements;
- New work planning that improves the FDA's inspection frequency and compliance work;
- Compliance policy and enforcement strategies that are "clear, current, outcome-based and effectively communicated;" and
- Laboratory optimization that fosters program alignment and cross-center collaboration.

The first report from the PAG should offer a look at how dramatic the changes will be; it is due to the commissioner in the next few months. Hamburg's memo highlights the "fundamental change" required of the agency as it is pulled in different directions to meet a steady stream of congressional requirements while, at the same time, struggling for funding.

The agency is still wrestling with the impacts of the ongoing federal budget sequestration — a factor that provides "little opportunity for the agency's tight budget to improve," the Alliance for a Stronger FDA said Sept. 6.

"Even if Congress's judgment is to increase FDA funding, with the sequester in place it is certain that FDA will face devastating and indiscriminate cuts" in fiscal 2014, it added, highlighting further impetus for achieving "optimal alignment" between the agency's directorates, centers and Office of Regulatory Affairs.

While there is bipartisan unity on shielding FDA user fees, movement on actually funding the agency has stalled. Agency appropriations bills for fiscal 2014 weren't considered by the full House and Senate before Congress broke for its month-long recess in August (*Generic Line*, Aug. 14).

To view Hamburg's memo to the PAG, go to www.fdanews.com/ext/files/09-06-2013-PAG.pdf. — Johnathan Rickman

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Biosimilar, *from Page 3*

Of the 19 state legislatures that have introduced biosimilar measures, GPhA says only North Dakota has passed intact the version supported by Amgen and Genentech.

The text of the California bill can be read at www.fdanews.com/ext/files/08-27-13-SB-598.pdf. — Melissa Winn

BRIEFS

FDA Issues Advair Diskus BE Guidance

The FDA Sept. 10 published draft guidance for industry providing recommendations on the design of bioequivalence (BE) studies to support ANDAs for fluticasone propionate/ salmeterol xinafoate.

Advair Diskus (fluticasone propionate/ salmeterol xinafoate), the registered listed drug (RLD) was approved by the FDA in August 2000. There are no approved ANDAs for it.

In December 2009, GlaxoSmithKline (GSK), manufacturer of the RLD, submitted a citizen petition requesting that the FDA withhold approval of any ANDA or 505(b)(2) application for generic oral inhalation products containing fluticasone propionate and/or salmeterol xinafoate unless certain conditions were satisfied, including conditions related to demonstrating BE.

The FDA said it is reviewing the issues raised in the petition and will consider any comments on the draft fluticasone propionate/ salmeterol xinafoate BE recommendations before responding to GSK's citizen petition.

The comment period for the guidance, docket no. FDA-2007-D-0369, ends Nov. 9, 2013. The draft guidance is available at www.fdanews.com/ext/files/09-9-13-fluticasone.pdf.

FDA Streamlining AG Reporting

The FDA is asking the Office of Management and Budget for the okay to streamline the way it collects information that makers of authorized generics are required to submit each year. The agency in a May 10 *Federal Register* notice said it plans to simplify the process through the use of automated collection techniques.

Drugmakers intending to market authorized generic drugs are required to submit information on them in their annual reports to the FDA under a final rule that took effect in 2010 (*Generic Line*, Feb. 17, 2010). The agency expects some 70 NDA holders to submit an estimated 500 annual reports this year notifying the FDA if an authorized generic is marketed. The agency said it did not receive any comments on the proposed changes.

Baxter, Coherus to Market Enbrel Biosimilar

Baxter and Coherus have entered into an exclusive agreement to develop and market a biosimilar to Amgen's blockbuster Enbrel (etanercept) for Europe, Canada, Brazil and other markets. Under the deal, Baxter will make an upfront payment of $30 million to Coherus, which will develop the biosimilar. Additional payments from Baxter of up to $216 million will be contingent upon Coherus' ability to reach certain milestones. The compact also allows for development and commercialization of an alternative biosimilar to etanercept, pending the results of clinical data.

Horizon, SkyePharma Sue Actavis Over Rayos

Horizon Pharma and SkyePharma have filed a patent infringement lawsuit in the U.S. District Court for the District of New Jersey against Actavis related to Watson's ANDA plans for Rayos containing 1 mg, 2 mg and 5 mg of the anti-inflammatory prednisone. Watson changed its name to Actavis in January (*Generic Line*, Oct. 24, 2012).

The lawsuit, filed Aug. 27, claims infringement of five patents listed in the FDA's Orange Book with the latest expiration Jan. 7, 2028.

Analysts Say Disputed Merck Patents Will Need to Prove Enablement

A patent lawsuit filed Aug. 30 by Gilead Sciences has analysts buzzing that its outcome will likely come down to U.S. patent laws' enablement requirement. To fulfill it, defendant Merck's disputed patents on compounds and methods of treating hepatitis C must adequately describe how to make and use them with enough detail that "one skilled in the art" is "enabled" to do so.

But analysts are skeptical that Merck can pull it off. Ruling in a similar case in March, the U.S.

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Patent and Trademark Office's Patent Trial and Appeal Board (PTAB) "provided important technical details that appear to favor Gilead," a report issued Sept. 3 by Leerink Swann states.

In the suit, filed in the U.S. District Court for the Northern District of California, Gilead accuses Merck of amending pending patent claims '499 and '712 to include compounds and methods of treating the hepatitis C virus (HCV) it learned were being developed by competitor Pharmasset, which Gilead later acquired.

Merck's HCV treatment Victrelis (boceprevir), a protease inhibitor approved by the FDA in 2011, has annual sales exceeding $500 million, according to the lawsuit.

Gilead filed an NDA for its own HCV treatment sofosbuvir on April 8, 2013. The nucleotide analogue NS5B polymerase inhibitor was granted priority review by the FDA on June 7. During the development of sofosbuvir, Merck became aware of competitive patent activities by Pharmasset and amended its claims "in an effort to exclude Pharmasset from the market or extract royalty payments in relation to potential future Pharmasset products," Gilead claims.

On July 29, less than three weeks after the '712 patent was issued, Merck's executive director of corporate licensing Pamela Demain began contacting Gilead about licensing rights to the '499 and '712 patents, the suit states. An Aug. 5 letter from Demain informed Gilead it could take a nonexclusive sublicensable license to the patents for commercialization of sofosbuvir. In return, Gilead would be required to pay a 10 percent royalty on the net sales of the drug "from the first sale of sofosbuvir until the expiration of the last to expire patent within the license patent rights."

Gilead is suing for declaratory judgment of non-infringement and invalidity of the '499 and '712 patents.

Analysts say Merck's patents don't appear to specifically provide examples of nucleotide polymerase inhibitors with 2'-methyl, 2'-fluoro-sustituted sugar, the class of nucleotides including sofosbuvir that Pharmasset focused on. That alone, however, won't disqualify the claims, they say.

In the March case between Gilead and Idenix, which holds similar patents on HCV treatments, the PTAB ruled that having only the structure of the nucleotides would require "undue experimentation" for the skilled artisan to make sofosbuvir, thus failing to meet enablement. In fact, one way to prepare similar compounds would lead to the exact opposite stereochemistry, the analysts say.

Merck spokesperson Lainie Keller confirmed to *Generic Line* that the company made the offer for the license of two of its patents. However, Keller declined to comment on the ongoing litigation. Requests to Gilead Sciences for comment were not returned. A lawyer representing Gilead told *Generic Line* he was not authorized to comment on the case. — Melissa Winn

Warner Chilcott, Mayne Pay Mylan $12 Million for Doryx Damages

Warner Chilcott and Mayne Pharma have agreed to pay $12 million to settle Mylan's claims for damages resulting from a patent suit targeting Mylan's generic version of the acne drug Doryx.

Mylan told the New Jersey U.S. district court in November that, in September 2011, it sought to recover damages under a $36 million bond posted by Warner and Mayne in the case. At the time, the court granted a permanent injunction to prevent an "at-risk" launch by Mylan of its generic Doryx (doxycycline hyclate).

The FDA approved Mylan's ANDA for doxycycline hyclate that same month.

In April 2012, the district court upheld the validity of the patent, but ruled that Mylan's proposed generic did not infringe it. A federal appeals court affirmed that decision.

Warner decided "not to petition for a rehearing," and the federal circuit court issued its judgment on Oct. 15, 2012, according to the company's quarterly report released in June.

Warner and Mayne initiated their suit against Mylan, Impax and Mutual Pharmaceuticals in 2008, claiming the companies' separate Paragraph IV ANDAs for Doryx infringed Mayne's '161 patent for modified-release drug preparation (*Generic Line*, Jan. 7, 2009). Warner has exclusive rights to market and sell products covered by the '161 patent in the U.S., including Doryx.

The loss of exclusivity for Doryx "resulted in a significant decline" in Warner's Doryx revenues for the year ended Dec. 31, 2012, the company's SEC filing states. The drugmaker recorded an impairment charge of $101 million in the quarter ended June 30, 2012, "related to its Doryx intangible asset," the filing adds.

In a separate lawsuit filed in July 2012, Mylan accused Warner of making minor changes to Doryx on three separate occasions as a way to impede generic competition. The changes offered little or no apparent medical benefit and were made to preserve Warner's monopoly, Mylan's complaint asserts.

The Federal Trade Commission filed an amicus brief in that case, urging the U.S. District Court for the Eastern District of Pennsylvania not to dismiss Mylan's lawsuit against Warner for alleged generic blocking tactics (*Generic Line*, Dec. 5, 2012). The commission said modifying products exclusively to avoid generic competition amounts to illegal exclusionary conduct. The case is still pending. — Melissa Winn

Sandoz Asks Court to Toss Charges for Generic Rapaflo

Citing Hatch-Waxman's safe harbor, Sandoz has asked a federal judge to throw out patent infringement charges lobbed against it after filing an ANDA for the prostate drug Rapaflo.

Kissei Pharmaceutical, Actavis and its subsidiary, Watson, have based several patent infringement claims on Sandoz's ANDA-filing activities. Sandoz made its case in a memo supporting a motion to dismiss recently filed in the U.S. District Court for the District of Delaware.

The innovators also claim future acts of infringement by Sandoz if the FDA approves its generic version of Rapaflo (silodosin) in the same form as is currently filed. But Sandoz dismissed those concerns as well, calling them "highly speculative" and unlikely to withstand the court's review.

Sandoz may prevail on that point. The same federal court dismissed similar allegations in AstraZeneca's patent suit against Mylan over its generic plans for Crestor (rosuvastatin calcium). Because FDA approval of Mylan's ANDA was years away and there was no certainty that the final approved generic would be in the same form after approval, the court tossed out the claims.

In a counterclaim, Sandoz is asking the court to find the patent in question invalid. The Rapaflo patent is licensed to Watson by Japanese drugmaker Kissei and covers certain aspects of silodosin preparation. It's set to expire in December 2018. — Melissa Winn

Novartis, *from Page 3*

Novartis' citizen petition argued against approval of ANDAs with the carved-out indication, saying safety information protected by patents relating to the osteoporosis indication would be omitted from a Paget's-only label, despite being pertinent to all patients.

In the interest of public health and ensuring adequate labeling for all products, Novartis believed "it was necessary and appropriate to bring these issues to the agency's attention and to do so transparently through the public citizen's petition process," a Novartis spokeswoman told *Generic Line*.

In response to the petition, the FDA consulted with internal experts and made modifications to the generic labels, then approved the ANDAs with modified labels, Novartis asserts in a petition for reconsideration of the FDA's petition response that was hand delivered to the FDA Aug. 23.

The agency further "criticized the timing of Novartis' petition in Section III of the response," the petition for reconsideration states.

The FDA's response says that Novartis first submitted an incomplete version of the petition on Feb. 28, submitting a corrected version the following day, one day before pediatric exclusivity on its '130 patent expired.

Novartis' claims in the petition required consultation with experts to make sure patients wouldn't be put at risk, which caused a "25-day delay in approval" for generic versions of Reclast, the agency maintains. The FDA approved Emcure and Dr. Reddy's ANDAs for the drug on March 29.

But Novartis contends it did not file the petition, which would be relevant solely to a carved-out Paget's-only label, until it learned at a Feb. 26 discovery hearing that some generic sponsors were seeking such approval.

No Press for Reversal

Novartis accepts the FDA's decision as it relates to the ANDA labeling issue, the spokeswoman told *Generic Line*.

The drugmaker's Aug. 23 petition for reconsideration does not seek a reversal of the FDA's denial of its citizen petition nor the approval of the ANDAs; it "solely concerns" *Section III: Misuse of Petition Process*, Novartis says. The company asks the FDA to "strike or modify that section," based on the facts and several documents with which it seeks to "supplement the record." The documents detail the timeline of Novartis' filing.

But Novartis' original petition raised issues worthy of consideration, as evidenced by the FDA's handling of it and modifications made to the generic labels based on the company's concerns, the drugmaker asserts. The company adds, "Novartis respects the FDA's concerns about the late filing of petitions that, unlike Novartis' Petition here, are intentionally delayed to prevent the agency from having adequate time to consider safety issues before approving ANDAs."

Novartis' Aug. 23 petition is at www.fdanews.com/ext/files/08-30-13-novartis-petition.pdf. — Melissa Winn

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