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Drug and Device 2014 Q2 Review

Inside

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The second quarter of 2014 has brought some significant developments in the drug and medical device arena. This white paper provides a general overview of selected developments, including significant FDA regulatory actions, court decisions, and other important developments in the second quarter (Q2) of 2014 in the fields of advertising and promotion, drug compounding, mobile medical apps, human antibiotics, e-cigarettes, and opiate abuse.

Significant FDA Regulatory Actions

On May 29, 2014, the FDA issued a final rule (79 FR 30716) implementing *administrative detention* authority with respect to human and animal use drugs. The detention authority is intended to protect the public by preventing distribution or subsequent use of drugs encountered during FDA inspections that are believed to be adulterated or misbranded, until the agency has had time to consider what action it should take concerning the drugs and initiate legal action, if appropriate.

The FDA estimates that between 20 million and 100 million parcels containing drugs enter the U.S. each year through international mail facilities, raising numerous public safety concerns with regard to adulterated and misbranded drugs. Consequently, on May 6, 2014, the FDA issued a proposed rule (79 FR 25758), implementing its ability to destroy a drug that has been refused admission into the U.S. under the federal Food, Drug, and Cosmetic Act and that has a value of $2,500 or less, or such higher amount as set by the Secretary of the Treasury through regulation. Comments were due by July 7, 2014.

In light of the safety concerns represented by hundreds of lawsuits, on May 1, 2014, the FDA proposed reclassification of surgical mesh for transvaginal pelvic organ prolapse (POP) repair from Class II to Class III (79 FR 24634). In the proposal, the FDA also seeks to reclassify urogynecologic surgical mesh instrumentation from Class I to Class II. Comments on the proposal are requested by July 30, 2014. The FDA concurrently published a proposed rule (79 FR 2464) that would require the filing of a premarket approval application for surgical mesh for transvaginal pelvic organ prolapse (POP) repair if it is successfully reclassified into Class III.

On June 3, 2014, OpenFDA, a new initiative designed to make it easier for web developers, researchers, and the public to access large, important publicly available datasets collected by the FDA, was launched by the agency. The OpenFDA initiative will make the FDA's publicly available data accessible in a structured, computer readable format that will make it possible for technology specialists to search, query, and extract large amounts of public information quickly and directly from FDA datasets. The initiative is

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designed to implement the May 9, 2013, Presidential Executive Order on Open Data and the HHS Health Data Initiative.

Court Decisions

On June 19, 2014, the Second Circuit held that a district court properly dismissed the antitrust claims of two wholesale distributors of Adderall XR® against Shire, LLC and Shire, U.S., Inc. (Shire), the holder of the patent on the drug. The Second Circuit rejected the theory that Shire's agreement with two competing manufacturers, Teva and Impax, to settle patent litigation by refraining from selling their generic versions of the drug for three years created any duty to supply the competitors with all the Adderall XR that the competitors' customers needed (*In re: Adderall XR Antitrust Litigation*).

On April 18, 2014, a federal district court in Atlanta held that a "reverse payment" settlement resolving patent infringement litigation between Solvay Pharmaceuticals—the marketer of brand-name testosterone replacement drug AndroGel—and would-be generic competitors Par Pharmaceutical Companies, Inc. and Paddock Laboratories, Inc. (ParPaddock) was not entitled to *Noerr-Pennington* immunity in an Federal Trade Commission (FTC) antitrust action, even though the underlying patent litigation was terminated by a consent judgment. The court denied the defendant's motion to dismiss the case, which was on remand from the U.S. Supreme Court. In June 2013, the U.S. Supreme Court ruled that the FTC could pursue the purported "pay-for-delay" settlements between Solvay and generic rivals Watson Pharmaceuticals (now Actavis, Inc.) and ParPaddock under a rule-of-reason analysis (*FTC v. Actavis, Inc.).* On remand, the district court ruled that "providing the consent judgment with *Noerr-Pennington* immunity would largely eviscerate the ruling in *Actavis*" (*In re AndroGel Antitrust Litigation (No. II)*).

On April 30, 2014, the Third Circuit affirmed a district court decision to preempt the strict-liability design-defect claims brought by many individuals from numerous states against the generic manufacturers of the osteoporosis drug, alendronate sodium. The district court had found that the claims were preempted because the generic manufacturers could not, under federal law, lawfully change either their labeling or the active ingredient design of their generic formulations and could not be expected to stop selling their drugs. Because the U.S. Supreme Court has stated that generic manufacturers have no control over the active ingredient design or labeling of their drugs and cannot be expected to exit the marketplace as a remedial action, and because the injured individuals failed to identify anything the generic manufacturers could do to reconcile their conflicting duties under state and federal law, the Third Circuit affirmed the district court's dismissal based on preemption (*In re Fosamax (Alendromate Sodium) Products Liability Litigation (No. II)*).

Advertising and Promotion

This June, the FDA issued three draft guidance documents on the advertising and promotion of drugs and devices.

- *Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices* outlines processes for drug manufacturers distributing new risk or safety information in medical publications intended for health care professionals and entities on existing, approved drugs or biologicals that further characterize the risks identified in approved labeling (*Notice*, 79 FR 33569, June 11, 2014).
- *Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices* provides that responses on a third party's platform must clearly identify the misinformation, address both positive and negative misinformation in the third party's statement, and be free of promotional material. The FDA makes it clear that firms are under no obligation to respond to misinformation on independent web sites or social media (*Notice*, 79 FR 34760, June 18, 2014).
- *Internet/Social Media Platforms with Character Space Limitations— Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices* presents considerations to illustrate FDA's thinking on factors that are relevant to the communication of benefit and risk information on Internet/social media platforms with character space limitations, such as messages on Twitter or "tweets," which are currently limited to 140 character 27 spaces per tweet and online paid search engines such as Google and Yahoo (*Notice*, 79 FR 34759, June 18, 2014).

In an interview with Wolters Kluwer, James A. Boiani, a Senior Counsel in the Health Care and Life Sciences Practice of Epstein Becker Green's Washington, D.C. office, stated that response to these three draft guidance documents by industry "has been mixed, but the fact that the FDA is re-starting the dialogue regarding its restrictions on free speech

by releasing these drafts is a promising sign." Boiani recommends that stakeholders "get *very* engaged and address [to FDA] the value of disseminating truthful and nonmisleading information that can help patients and physicians make better decisions."

Drug Compounding

On April 1, 2014, the FDA published (79 FR 18297) a draft guidance titled, "Fees for Human Drug Compounding Outsourcing Facilities Under Sections 503B and 744K of the FD&C Act." The guidance is intended to implement and explain the registration, inspection, and user fee requirements of the Compounding Quality Act, Title I of the Drug Quality and Security Act (DQSA) (P.L. 113-54), which established a new category of facilities called "outsourcing facilities."

Then, on July 1, 2014, the FDA issued several documents regarding compounded drugs for human use, including a proposed rule, a draft interim guidance, a final guidance, and two revised requests for nominations for the bulk drug substances lists.

- The *proposed rule* would revise the FDA's current list of drug products that may not be compounded because the drug products have been withdrawn or removed from the market because they were found to be unsafe or ineffective. The proposed rule would modify the description of one drug product on the list and add 25 drug products to the list. The list would apply to both compounders and "outsourcing facilities" seeking to compound drugs under sections 503A and 503B of the FD&C Act, respectively.
- The *draft interim guidance* describes the FDA's expectations regarding compliance with current good manufacturing practice (CGMP) requirements for facilities that compound human drugs and register with the FDA as "outsourcing facilities" under section 503B. The guidance focuses on general safety and sterility assurance.
- The *final guidance* is for individuals or pharmacies that intend to compound drugs under section 503A. The guidance restates the provisions of section 503A, describes the FDA's interim policies, and contains a non-exhaustive list of potential enforcement actions.
- The two notices reopen the nomination process for two lists of bulk drug substances (active pharmaceutical ingredients) that may be used to compound drug products. One *list is for drug products compounded in accordance with section 503A*, and the other list is for *drug products compounded in accordance with section 503B* of the FD&C Act.

Boiani states that in the second quarter we continued to see the "FDA taking action against compounding pharmacies – it has issued five or six warning letters this quarter under the auspices of the Compounding Quality Act." According to Boiani, the "FDA seems hell bent on shutting compounding pharmacies down and/or cajoling them into registering as outsourcing facilities, even while it refuses to tell stakeholders how much of the Compounding Quality Act will work; FDA has a firm policy of refusing to meet with individual stakeholders, and has been unwilling to engage in dialogue with limited exceptions. This stands in stark contrast to

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FDA's rollout of regulation for mobile medical applications, where the Agency has been good about engaging with the public and having a good discussion. In light of what prompted enactment of the Compounding Quality Act (a major tragedy), the important role that compounding plays in the practice of medicine, and concerns about compounding providing a means to circumvent the drug approval process, I don't understand why the Agency won't engage more. Engagement is what good government is all about."

Mobile Medical Apps

Boiani believes the Center for Devices and Radiological Health's release of the draft guidance *Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices - Draft Guidance for Industry and Food and Drug Administration Staff*, where it proposes to deregulate certain software devices called Medical Device Data Systems, "reflects a positive trend, with the FDA taking a lighter touch [in stark contrast

to its regulation of compounding pharmacies] when it comes to regulating software apps…I think in recognition that for the industry to flourish and for patients to realize the benefits of mobile medical applications [the FDA] needs to give it room to grow."

Human Antibiotics

On June 5, 2014, the FDA issued a final rule (79 FR 32464) listing 21 "qualifying pathogens," which are pathogens that have "the potential to pose a serious threat to public health," pursuant to a requirement under the Generating Antibiotic Incentives Now (GAIN) title of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144). GAIN's purpose is to encourage the development of new antibacterial and antifungal drugs to treat serious or life-threatening infections. For example, it provides incentives for drugs designated as "qualified infectious disease products" (QIDPs), allowing them an additional five years of exclusivity and also allowing QIDP applications to receive priority review and be designated as a fast-track product.

Boiani sees the GAIN Act, the issuance of this list of 21 qualifying pathogens, and the FDA's recent approval of two GAIN antibiotics as an indication that the "approval of human antibiotics seems to be moving forward." According to Boiani, "there is still a lot more work to do to open up the pipeline for these products—which is a pressing health concern—but the news this month is good stuff."

E-Cigarettes

Lawmakers and the FDA have been taking action on the regulation of e-cigarette advertising during the second quarter of 2014. Virginia's Senate Bill 96, signed into law on March 27, 2014, effectively prohibits the sale, distribution, or purchase of any tobacco product, nicotine vapor product, or alternative nicotine products to or by an individual under the age of 18 years, beginning July 1, 2014. The bill amends and reenacts section 18.2-371.2 of the Code of Virginia.

On April 7, 2014, a group of Democrat senators urged the FDA and FTC to take action against electronic cigarette (e-cigarette) manufacturers who are making unfounded and false claims in their advertising, including claims that the devices can help conventional cigarette smokers quit. According to a report by a coalition of Democrat senators and representatives, a large number of e-cigarette companies promote and offer free samples of e-cigarettes at youth-oriented events. The report investigated the practices of nine frequently sold e-cigarette brands to address growing concerns over e-cigarette regulation and marketing.

As a result the mounting evidence of public health concerns, on April 24, 2014, extending its regulatory authority from cigarettes to e-cigarettes, the FDA proposed new regulations (79 FR 23142) that would ban the sale of e-cigarettes to children and teens under 18 years of age. Photo identification as proof of age would be required to purchase e-cigarettes. In addition to the ban of e-cigarette sales to minors, pipe tobacco such as hookahs (water pipes) also would fall under the expanded regulatory purview of the FDA. The FDA also would revisit the issue of the display of health warnings on cigarette tobacco, roll-your own tobacco, and covered tobacco product packages in advertisements. The FDA also asked for public comment on whether premium cigars — hand-rolled with a tobacco leaf as a wrapper—should be placed in a special separate category not subject to the FDA's authority.

Opiate Abuse

Controversy continues regarding the FDA's approval of the opioid prescription drug Zohydro™ ER, despite an advisory committee's overwhelming vote recommending that the drug be rejected. The drug, which is the only hydrocodone product that is currently subject to Schedule II controls by the Drug Enforcement Administration, is used to treat patients that require around-the-clock, long-term opioid treatment for severe pain and for which there are no adequate alternative treatment options available.

On April 7, 2014, Zogenix, Inc. filed suit seeking to set aside the Governor of Massachusetts' emergency declaration that immediately prohibited the prescribing and dispensing of Zohydro™ ER. Governor Deval Patrick issued an emergency declaration on March 27, 2014, in response to a growing opioid addiction problem within the state. On April 15, 2014, however, a federal court in Massachusetts enjoined the enforcement of the ban on sales of Zohydro™ ER. The court ruled that the state's action was preempted by the FDA's approval of the drug (*Zogenix, Inc. v Patrick*).

Then, on May 6, 2014, Pennsylvania State Representative Gene DiGirolamo (R-18th Legislative District) introduced House Bill 2203 into the General Assembly of Pennsylvania. The bill, if passed, would effectively classify Zohydro™ ER as a schedule I controlled substance within the state, thereby placing a number of rules and regulations in place with regard

to the handling, sale, and use of the product. DiGirolamo's concerns echo the consensus among 29 state Attorney Generals who sent a letter to FDA Commissioner Margaret Hamburg, M.D. last December, requesting that the agency reconsider its approval of Zohydro™ ER. They wrote, "We believe your approval of Zohydro™ ER has the potential to exacerbate our nation's prescription drug abuse epidemic because this drug will be the first hydrocodone-only opioid narcotic that is reportedly five to ten times more potent than traditional hydrocodone products, and it has no abuse-deterrent properties."

Finally, on June 9, 2014, BioDelivery Sciences International, Inc. (BDSI) received approval from the FDA for its new drug BUNAVAIL™ (buprenorphine and naloxone) buccal film (CIII), which represents a new efficient approach to drugs aimed at the treatment of opioid dependence. The drug, which is expected to be available late in the third quarter of 2014, uses a delivery method known as buccal administration, in which the drug sticks inside the cheek while it is being absorbed. According to BDSI, this new delivery method is a vast improvement over traditional sublingual (under the tongue) delivery methods because it allows a patient to continue his or her daily activities while the drug is being absorbed.

See The risk of opioid abuse, addiction, and overdose in treatment of chronic pain and Should States Limit Access to FDA-Approved Opioids?

Conclusion

Moving forward into Q3 and Q4 of 2014, Boiani "would keep an eye on advertising & promotional policies at FDA and associated First Amendment issues that will have a huge impact on how products are marketed." Boiani also "expects to see more from FDA on the issue of combination product regulation (*e.g.*, combinations of drugs with medical devices, such as drugs and injector systems), with some guidance on combination product good manufacturing practices being released later this year." According to Boiani, "there are also a bunch of questions swirling around FDA regulation of *in vitro* diagnostics, such as regulation of companion diagnostics (diagnostics that are designed to guide the use of drug therapies for cancer and other life-threating conditions); problems with the Clinical Laboratory Improvement Amendments (CLIA) Waiver process (the process manufacturers' used to bring novel diagnostic tests to the point of care, which is good for patients and physicians); the development of a 'transitional IVD' pathway (a route to bring diagnostic tests to market more quickly); and laboratory developed test issues…the list goes on and on." Boiani is "not sure what will get resolved within the next 6 months," but he is "hopeful that we'll see at least two or three more antibiotic drug approvals within the next six months, because those are products we desperately need."

In addition to the ban of e-cigarette sales to minors, pipe tobacco such as hookahs (water pipes) also would fall under the expanded regulatory purview of the FDA.