

FDA Developments In 2015 And What's To Come In 2016

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2015 ushered in several important events and key regulatory developments that significantly impacted the pharmaceutical and medical device industry. Some developments were contentious, and are likely harbingers of things to come in 2016. Below, we present our picks for the top regulatory developments of the past year, and some predictions for 2016.

A Change at the FDA's Helm

U.S. Food and Drug Administration Commissioner Margaret Hamburg retired at the end of March 2015.[1] Dr. Hamburg's influence on the FDA resulted in many positive developments, including: improved agency morale, increased numbers of drug approvals, record numbers of orphan drug approvals, decreased drug approval times, implementation of a biosimilar approval process, spurring desperately needed antibiotic development through implementation of the Generating Antibiotic Incentives Now Act and encouraging the development of combination drugs for diseases like AIDS, hepatitis and cancer by interpreting the law to grant five years of exclusivity for certain fixed dosage combination drugs.[2]



Charles Andres

Duke cardiologist, Robert Califf, who is replacing Dr. Hamburg, has served as a Deputy Commissioner of the FDA since early 2015, and has an impressive track record. He was the founding director of the Duke Clinical Research Institute, ran the Duke Translational Medicine Institute, spearheaded Merck's ZETIA six-year IMPROVE-IT study and served on the board of biotech startup Portola Pharmaceuticals. We believe, and hope, Dr. Califf will continue to build upon the positive changes and successes at the FDA overseen by Dr. Hamburg.

Increased Number of Drug Approvals

The FDA approved 45 drugs with never-before-sold ingredients in 2015, edging past the 2014 tally of 41, which had been the highest number since 1996.[3] The rising figures suggest that industry is focusing on drugs for rare and hard-to-treat diseases, which often come with the ability to use streamlined reviews, extra patent protections and higher prices. The FDA notes that "[f]rom 2006 through 2014 it averaged about 28 novel new drug approvals per year." [4] The trend to increased approvals should continue as pharmaceutical companies pick better drug candidates based on use of e.g., diagnostic assays to streamline clinical trials and maximize the potential for investigational compounds to be found safe and effective.[5]

Laboratory Developed Tests

The FDA has indicated it will begin regulating at least high-risk LDTs[6] in 2016. It has been estimated that there are currently 11,000 LDTs offered by 2,000 laboratories in the U.S. The FDA defines an LDT “as an [in vitro diagnostic device] IVD that is intended for clinical use and designed, manufactured and used within a single laboratory.”[7] Although the FDA asserts it has had the legal authority to regulate LDTs as medical devices since the Medical Device Act of 1976, the agency exercised its discretion and elected not to regulate these products. The FDA now asserts that times have changed. Specifically, the FDA asserts that LDTs are now often independent of the health care delivery entity, are frequently manufactured with components and instruments that are not legally marketed for clinical use and rely on high-tech instrumentation and software to generate results and clinical interpretations. The FDA also believes that LDTs are increasingly critical for clinical management decisions for high-risk diseases and personalized medicine. The FDA “identified problems with several high-risk LDTs including: claims that are not adequately supported with evidence; lack of appropriate controls yielding erroneous results and falsification of data.”[8] Accordingly, the FDA now has decided to exercise its statutory authority to regulate LDTs. The FDA’s decision will directly and significantly impact the estimated 2,000 laboratories offering approximately 11,000 LDTs.

Based on guidance that the FDA says will be finalized in the coming months, the agency will take a risk-based approach to regulation and prioritization of LDTs. The FDA’s regulation of LDTs through guidance documents raise important issues, including whether: 1) The FDA has the statutory authority to regulate LDTs; 2) if the FDA is complying with the Administrative Procedure Act by using guidances, instead of notice and comment rule making; 3) the FDA’s basis for believing that it is now necessary to regulate LDTs; and 4) whether the proposed regulations will stifle innovation. We expect the FDA’s regulation of LDTs to be challenged in the courts and to receive significant lobbying to lawmakers. The FDA’s proposed regulation of LDTs has the potential to remake the LDT provider landscape.

Five Year Market Exclusivity for an Isolated Component of a Previously Approved Mixture

In 2014, recognizing the importance of fixed dose combination drugs, the FDA changed its interpretation of the law to allow five years of market exclusivity for fixed dose combination drugs that contained at least one new active ingredient that had not been previously FDA approved.[9] In 2015, the door was opened for five years of market exclusivity for some drugs that are isolated components of a previously FDA approved mixture.

This new interpretation of law was raised by Amarin, with its drug Vascepa. By way of background, in 2004 the FDA approved Amarin’s drug Lovaza, whose active ingredient was a mixture of omega-3 esters, including EPAe. Although “portions of Lovaza’s label refer to the specific components of the mixture, there is no dispute that its sole ‘active ingredient’ is the mixture as a whole.”[10] Based on its reading of the statute and the FDA’s regulations, Amarin contended that EPAe had never been previously approved by the FDA as an active ingredient. Amarin argued that Lovaza’s mixture-as-active-ingredient was different from EPAe as a sole active ingredient for purposes of determining exclusivity.

Months after Amarin’s EPAe was approved as the drug Vascepa, FDA denied five years of market exclusivity based on a new ‘one-to-many’ framework analysis. This one-to-many framework, implemented without previous notice and comment rule making or guidance, did not perform the ‘active ingredient’ to ‘active ingredient’ comparison as required by statute. Amarin took the FDA to court. The U.S. District Court for the District of Columbia vacated and remanded the FDA’s decision denying five years of new chemical entity exclusivity for Vascepa. Thus, the District Court opened the

door for five years of market exclusivity for some drugs that are isolated components of a previously FDA approved mixture.

Scheduled Drugs, Exclusivity and Patent Term Extension

When a new drug is first approved by the FDA, the drug is entitled to a period of market exclusivity. For a subset of these new drugs, the FDA will determine if the product has the potential to be abused, and if it can be abused, the agency will make a scheduling recommendation to the Drug Enforcement Administration. Scheduling a drug is, among other things, a way of classifying the addictive potential of the drug. The FDA's scheduling recommendation is legally binding on the DEA.

A nonscheduled new drug can be marketed upon FDA approval. Thus, for nonscheduled new drugs, the market exclusivity and drug marketing start and run concurrently with approval. In comparison, for new drugs that must be scheduled, the FDA requires the sponsoring company to attest that it will not market the new drug until the DEA makes a “final scheduling decision” — i.e., until the DEA schedules the drug. Traditionally, there has been no deadline for the DEA to make a scheduling decision. Therefore, the FDA can approve a new drug as safe and effective, but patients and physicians must wait to access the newly approved therapy with no expectation of a reasonable timetable in which access will be granted. In addition to DEA scheduling delays denying patient and physician access to a new FDA-approved drug, the DEA's scheduling delay historically meant that the drug's innovator could not market the approved drug until it was scheduled, even though the market-exclusivity clock started upon FDA approval.

On Nov. 25, 2015, President Obama signed into law the Improving Regulatory Transparency for New Medical Therapies Act (H.R. 639).[11] H.R. 639 resets the drug approval date to the later of: i) the date of FDA approval of the drug; or ii) the date of issuance of the interim final rule scheduling the drug. By resetting the approval date to the later of FDA approval or DEA scheduling, H.R. 639 remedies the situation where drug marketing is delayed while the market-exclusivity clock runs. This is a significant development for innovators developing new drugs that require scheduling. H.R. 639 applies to new small-molecule drugs, biologics and animal drugs that the FDA determines require scheduling.

In addition, H.R. 639 modifies the patent term extension (PTE) statute (35 U.S.C. § 156) to provide that the deadline for filing a PTE application is the later of FDA approval of the new drug or “the date of issuance of the interim final rule controlling the drug under Section 201(j) of the Controlled Substances Act.” This is another significant development for innovators, as it may provide more time to: i) gain allowance of a patent that could be extended; and ii) thereby allow greater flexibility and optimization in life cycle management strategies.

Dietary Supplements

In the last 20 years, dietary supplement sales have climbed from \$6 billion to \$35 billion annually.[12] The growth of the supplement industry corresponded with the FDA issuing an increasing number of warning letters, supplement recalls and other corrective actions. The FDA has seen increasing supplement adulteration (e.g., a supplement for erectile dysfunction containing the prescription drug sildenafil citrate (Viagra)) and misbranding. To better regulate supplements and protect consumers,[13] the FDA created the Office of Dietary Supplement Programs (ODSP). The FDA envisions that ODSP “will enhance the effectiveness of dietary supplement regulation by allowing ODSP to better compete for government resources and capabilities to regulate this rapidly expanding industry.”[14] The creation of ODSP will likely result in further regulatory scrutiny of this growing industry.

First Amendment Protections and Off-Label Drug Promotion

On Aug. 7, 2015, the U.S. District Court for the Southern District of New York released its opinion in *Amarin Pharmaceuticals Ireland Ltd. v. FDA*,^[15] which addressed whether truthful, non-misleading off-label promotion of an FDA-approved drug constitutes protected First Amendment speech.

For years, the FDA has taken the position that a drug or medical device manufacturer who proactively promotes an approved product for an unapproved (off-label, or unlabeled) use violates the Federal Food, Drug and Cosmetic Act (FDCA). According to the agency, such off-label promotion misbrands the product. A misbranding charge can result in a felony conviction, with a significant term of imprisonment and monetary fine. Amarin sought to proactively promote off label its FDA-approved drug Vascepa for lowering triglycerides (TGs) in patients having TG levels between 200 and 499 mg/dL of blood and who are already on statin therapy — an unapproved and off-label use. Vascepa's ability to safely lower triglycerides in this patient population was undisputed and confirmed by the FDA. However, the FDA rejected Amarin's request for approval for this new indication. In its complete response letter, the FDA affirmatively warned Amarin that Vascepa “may be considered to be misbranded ... if it is marketed [for this indication] without approval of [a] supplemental application.”^[16]

Amarin sued the FDA in district court, requesting preliminary relief on First Amendment grounds: Amarin wished to proactively make truthful nonmisleading statements to doctors regarding Vascepa but was inhibited from doing so by the FDA's threat to bring a misbranding action based on the off-label promotion. In rejecting the FDA's position on all counts, the district court held that its “considered and firm view is that [under *Caronia*], the FDA may not bring [a misbranding] action based on truthful promotional speech alone, consistent with the First Amendment.”^[17]

This is a clear victory for both the pharmaceutical and medical device industries. However, important questions remain, including: what is the overall impact of this and earlier decisions — which apply to truthful and nonmisleading off-label promotion of lawfully approved drugs and medical devices? Going forward, drug and device makers must attempt to determine what constitutes truthful and nonmisleading speech, especially in light of the district court's warning that this could change over time and with new facts.

Biologics Price Competition and Innovation Act and the Patent Dance

On July 21, 2015, the U.S. Court of Appeals for the Federal Circuit issued its holding in *Amgen Inc. v. Sandoz Inc.*, 2015-1499 (Fed. Cir. 2015). The Federal Circuit's decision marked a significant development in the long-running battle between Sandoz and Amgen over Sandoz's attempt to market a biosimilar filgrastim (Zarxio) product.

In a case of first impression, a divided Federal Circuit panel addressed whether: i) a biosimilar applicant may elect not to disclose its abbreviated biologics license application (aBLA) and manufacturing information to the reference product sponsor (RPS) under the BPCIA; ii) when notice of commercial marketing must be given to the RPS; and iii) whether, in the case of non-aBLA disclosure, notice is mandatory.

Important BPCIA clarifications emerged from the majority opinion by Judge Alan D. Lourie. The first clarification addressed whether a biosimilar applicant may elect not to disclose its aBLA and manufacturing information to the RPS, subject only to the remedies and consequences set forth in 42 U.S.C. § 262(l)(9)(C) and 35 U.S.C. § 271(e)(2)(C)(ii) (e.g., to being sued for infringement).^[18]

The BPCIA “explicitly contemplates that [an applicant] might fail to disclose the required information by the statutory deadline ... [and] specifically sets forth the consequence ... [that] the RPS may bring an infringement action ...”[19] Buttressing its statutory interpretation, the Federal Circuit also noted that once the RPS “brings an infringement suit ... it can access the required information through discovery.”[20] “Because Sandoz took a path expressly contemplated by the BPCIA, it did not violate the BPCIA by not disclosing its aBLA and the manufacturing information by the statutory deadline.”[21]

Next, the Federal Circuit addressed the notice of commercial marketing provisions of the BPCIA, specifically whether the 180-day commercial marketing notice to the RPS can only be given after a follow-on biological product is licensed by the FDA. Noting that the statutory language “compels such an interpretation” and that “notice, to be effective under the statute, must be given only after the product is licensed by the FDA,” the Federal Circuit agreed with Amgen: “[A]n ... [aBLA] applicant may only give notice of commercial marketing after the FDA has licensed its product.”[22]

The Federal Circuit also concluded that the notice provision was mandatory for section (k) applicants who fail to provide their aBLAs and manufacturing information to the RPS by the statutory deadline.

Two Year Moratorium on Medical Device Excise Tax

The Patient Protection and Affordable Care Act's[23] 2.3 percent medical device excise tax was contentious even before taking effect on Jan.1, 2013. Under the ACA, medical device manufacturers and importers are required to pay a 2.3 percent excise tax on sales of medical devices.[24][25] Although a small group of medical devices were exempt (e.g., eye glasses, contact lenses, hearing aids and certain other devices generally purchased by the public at retail for individual use),[26] most devices remained subject to the excise tax. The tax has invoked strong objections, with some stakeholders arguing that the tax hit small and start-up medical device manufacturers unduly hard, cost jobs and limited innovation of new medical devices.

The Consolidated Appropriations Act of 2016,[27] signed on Dec. 18, 2015, by President Obama, suspends the 2.3 percent medical device excise tax beginning on Jan. 1, 2016, with the suspension ending on Dec. 31, 2017.[28] This two-year moratorium is welcome news for medical device manufacturers and importers, especially for small medical device manufacturers and start-ups.

Four Predictions for 2016

1. The FDA will begin regulating high risk LDTs early in 2016. This will be contentious and we expect that the FDA’s regulation of LDTs will be challenged in the courts. The FDA’s regulation of LDTs has the potential to reshape a significant portion of diagnostic testing industry landscape.
2. This prediction is a long shot based and is based on information from sources on the Hill. Congress may grant regulatory exclusivities to diagnostic tests. Diagnostic tests are the cornerstone of personalized medicine. Personalized medicine is the future of medicine. Unlike drugs, traditional medical devices and diagnostic tests, which the FDA regulates, do not get FDA regulatory exclusivities. Diagnostic tests and medical devices therefore rely on patents to protect market exclusivity.[29] Recent developments in patent subject matter eligibility law have made it more difficult for diagnostic methods, but not traditional medical devices, to surmount the historically low patent subject matter eligibility hurdle.[30] These developments, initiated by the U.S. Supreme Court, have profound, negative implications for patients, doctors, test developers and providers and health care payers (including

insurance companies and the federal government). To attempt to better balance the situation, Congress may enact legislation giving regulatory exclusivities to diagnostic tests.

3. The FDA, in conjunction with the Department of Justice and state attorney generals, will continue its enforcement actions against companies, and there will be an increased focus on individuals, including CEOs of regulated companies[31]

4. Orphan drug approvals will continue to increase. Orphan drugs treat diseases that affect less than 200,000 persons in the U.S. Orphan drugs come with several advantages, including: seven years of marketing exclusivity, a price premium of approximately 120 percent over nonorphan drugs, a tax credit, the potential for clinical trial grants and eligibility for approval accelerating tools (e.g., breakthrough designation accelerated approval).[32] Also, there are an estimated at least 8,000 orphan diseases that have a genetic basis and for which treatment does not exist or is inadequate. For all of these reasons, pharmaceutical manufacturers will continue to develop new drugs to target orphan diseases.

Conclusion

2015 was an eventful year for both the FDA and the regulated industry. Many of the developments are, or hold the potential, to be positive for medical device and pharmaceutical companies. Other developments are contentious and will continue to play out in 2016.

—By David Hoffmeister, Vern Norviel, Prashant Girinath, Chris McAndrew and Charles Andres, Wilson Sonsini Goodrich & Rosati PC

David Hoffmeister is a partner in Wilson Sonsini's Palo Alto, California, office and former senior counsel for drug and device law at Syntex USA.

Vern Norviel is a partner in Wilson Sonsini's San Diego, California, office and former general counsel and corporate secretary of Perlegen Sciences Inc.

Prashant Girinath is an intellectual property specialist in Wilson Sonsini's Washington, D.C., office.

Chris McAndrew is a patent agent and law clerk in Wilson Sonsini's Washington, D.C., office.

Charles Andres is an associate in Wilson Sonsini's Washington, D.C., office.

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[1] D. M. Hoffmeister et al., "There's A Lot To Like About Hamburg's Legacy At The FDA", Law360, Feb. 9, 2015.

[2] Id.

[3] "Novel New Drugs Summary 2015", FDA, Jan. 5, 2016.

[4] Id.

[5] Many of these approvals have been accelerated by priority review and other expediting programs implemented by FDA. For an information presentation, see J. K. Jenkins, M.D., Director Office of New Drugs, "CDER New Drug Review: 2015 Update", FDA, Dec. 14, 2015.

[6] See, e.g., D. M. Hoffmeister et al., "FDA Takes Another Step Toward Regulating LDTs," Law360, Oct. 9, 2014.

[7] "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" at page 5. FDA's LDT guidances are available electronically here and here.

[8] "Laboratory Developed Tests," FDA, Nov. 11, 2015.

[9] See, e.g., V. Norviel et al., "New Exclusivity for Fixed-Dose Drugs Will Help Small Firms," Law360, April 28, 2014.

[10] D. M. Hoffmeister et al., "Amarin Decision Opens Door To Longer Exclusivity Periods," Law360, June 12, 2015, and citations therein.

[11] See, e.g., D. M. Hoffmeister et al., "New Law Remedies Partial Loss of Drug Marketing Exclusivity Period Caused by U.S. DEA Scheduling Delays," WSGR Alert, Dec. 2, 2015.

[12] See, e.g., Z. Brennan, "FDA Unveils New Office of Dietary Supplement Programs," RAPS Regulatory Focus, Dec. 21, 2015.

[13] FDA recently announced the seizure of nearly 90,000 bottles of dietary supplements labeled as containing kratom – FDA describes kratom as "a botanical substance that could pose a risk to public health and have the potential for abuse." See "U.S. Marshals seize dietary supplements containing kratom," FDA, Jan. 6, 2016.

[14] "FDA Creates the Office of Dietary Supplement Programs and Announces New Nutrition Office Leadership," FDA, Dec. 21, 2015.

[15] *Amarin Pharmaceuticals Ireland Ltd. v. FDA*, 14-cv-00324 (Dist. Court, Dist. of Columbia, 2015).

[16] D. M. Hoffmeister et al., "District Court Holds That FDCA Does Not Prohibit and Criminalize Truthful Off-Label Promotion of FDA-Approved Prescription Drugs," WSGR Alert, Aug. 11, 2015, and citations therein.

[17] *Id.*

[18] See, e.g., V. Norviel et al., "Federal Circuit Amgen Case Clarifies Important Aspects of the Biologics Price Competition and Innovation Act," *Generic Pharma 2.0*, July 22, 2015, and citations therein.

[19] *Id.*

[20] *Id.*

[21] *Id.*

[22] Id.

[23] Pub. L. No. 111-148, 124 Stat. 119 (2010); Pub. L. 111-152, 124 Stat. 1029 (2010); collectively the ACA.

[24] Pub. L. 111-152, 124 Stat. 1029 (2010), Section 1405.

[25] A “taxable medical device” is one that is listed as a device with the U.S. Food and Drug Administration under Section 510(j) of the Federal Food, Drug and Cosmetic Act, and 21 C.F.R. part 807.

[26] I.R.C. § 4191(b)(2); Treas. Reg. § 48.4191-2(b). See also “Medical Device Excise Tax: Frequently Asked Questions,” IRS, Feb. 3, 2014.

[27] H.R. 2029. The CAA runs 887 pages and is partitioned into Divisions A-Q.

[28] CAA, Division Q, Subtitle C, Part 2, Section 174.

[29] Although diagnostic tests do not get FDA regulatory exclusivity, diagnostic tests that receive FDA premarket approval (PMA) are eligible for patent term extension. See, e.g., V. Norviel et al., “Patent Term Adjustment and Patent Term Extension: Valuable Tools to Prolong Patent Protection Through Careful Vigilance,” Life Sciences Report, 2014.

[30] For one perspective on patent subject matter eligibility, see, e.g., M. Skubatch et al., Brief of Amici Curiae Amaranthus Bioscience Holdings Inc., Personalis Inc. and Population Diagnostics Inc. in Support of Appellants' Petition for Rehearing En Banc.

[31] See, e.g., D. M. Hoffmeister et al., “Off-label Promotion — Minimizing the Risk,” FX Conferences, Oct. 16, 2015.

[32] See, e.g., D. M. Hoffmeister et al., “Reflections On The Remarkable Rise Of Orphan Drugs,” Law360, Jan. 28, 2015.