Pharmaceutical Law

Regulation of Research, Development, and Marketing

2013 Cumulative Supplement

Editor-in-Chief

Michael E. Clark
Duane Morris LLP
Houston, Texas

Chapter 1: Statutory and Regulatory Controls for Drug Development

Frederick R. Ball and Elinor L. Hart

Duane Morris LLP

AMERICAN BAR ASSOCIATION
Health Law Section

The American Bar Association
Health Law Section

Bloomberg BNA

Bloomberg BNA, Arlington, VA

Library of Congress Cataloging-in-Publication Data

Pharmaceutical law : regulation of research, development, and marketing / editor-in-chief, Michael E. Clark.
p. cm.
ISBN 978-1-57018-576-2 (alk. paper)
1. Pharmacy--Law and legislation--United States. 2. Drugs--Law and legislation--United States. 3. Pharmaceutical industry--United States. 4. Drug development--United States. I. Clark, Michael E., 1956- II. Title.

KF2915.P4P495 2007
344.7304'16--dc22

2007033206

Published by Bloomberg BNA
1801 S. Bell Street, Arlington, VA 22202
bna.com/bnabooks

ISBN: 978-1-61746-323-5
Printed in the United States of America

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Statutory and Regulatory Controls for Drug Development

*Frederick R. Ball and Elinor L. Hart**

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*Frederick (Rick) R. Ball is a partner at Duane Morris LLP, Boston, Massachusetts. Elinor L. Hart is an associate at Duane Morris LLP, Chicago, Illinois. The authors thank James E. Szalados, who prepared an earlier version of this chapter.

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I. Regulation of Pharmaceuticals in the United States

B. The FDA's Approval Process for New Drugs

1. How the New Drug Application Process Operates

On September 19, 2011, the U.S. Food and Drug Administration (FDA) issued a Compliance Policy Guide (CPG) titled "Marketed Unapproved Drugs,"[1] which revises the FDA's 2006 CPG regarding the same topic. The CPG not only sets forth the FDA's current view on enforcement action related to these drugs,

[1]U.S. Dep't Health & Human Servs., Food & Drug Admin., Marketed Unapproved Drugs—Compliance Policy Guide (Sept. 19, 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070290.pdf.

but also outlines potential incentives for manufacturers to voluntarily file a New Drug Application (NDA). The CPG sets forth several categories of marketed unapproved drugs that the FDA views as enforcement priorities. Consistent with the FDA's goal of ensuring that all products comply with the approval provisions of the Federal Food, Drug, and Cosmetic Act (FDCA)—namely that all drug products demonstrate both safety and effectiveness—the FDA stated that priority products will be

- drugs with potential safety risks;
- drugs that lack evidence of effectiveness;
- "Health Fraud Drugs," meaning drugs that have not been proven safe and effective for their promoted benefits;
- drugs that otherwise challenge the NDA or over-the-counter (OTC) review systems;
- drugs that otherwise violate the FDCA; and
- drugs that have been reformulated to avoid FDA action, but that remain noncompliant.[2]

Regardless of these broad categories, the FDA has stated that products involved in Drug Efficacy Study Implementation (DESI) proceedings or OTC monograph proceedings are generally exempt from any enforcement action.

In addition, the FDA indicated that it will evaluate products on a case-by-case basis to determine whether some period of continued marketing is warranted. Thus, a "grace period" may exist, depending upon: the effects on the public; the difficulty of performing the necessary scientific studies on the product; the relative burden on the affected parties; the FDA's resources; and other special circumstances. The CPG further provides for a special circumstance where the variable grace period described above can result in a de facto exclusivity period for the manufacturer who first complies with the FDCA. The FDA recognizes that a company may file an NDA for a product that other companies are marketing without approval. For such drugs, the FDA has indicated that it normally intends to allow for a one-year grace period before initiating any enforcement action against unapproved drugs that remain on the market. However, this one-year period is variable and will be decided on a case-by-case basis. If the grace period is shorter, according to the CPG, "the more likely it is that the first company to obtain approval will have a period of de facto market exclusivity before other products obtain approval."[3]

3. When an Abbreviated New Drug Application Is Required

c. Marketing Generic Drugs and Anticompetitive Activity

Notwithstanding the final rule, the Federal Trade Commission (FTC), generic manufacturing industry, and the brand pharmaceutical industry continue to debate issues regarding these "Pay for Delay" contracts.[4] The FTC

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[2]*Id.*

[3]*Id.*

[4]In "Pay for Delay" contracts, the brand manufacturer enters into a business relationship with the generic manufacturer whereby the latter agrees to postpone entry into the market based

continues to challenge these agreements, but with limited success, and the Attorney General of the United States in 2009 took the position that these agreements violate antitrust laws.[5]

For example, in *In re Ciprofloxacin Hydrochloride Antitrust Litigation*,[6] indirect purchasers and advocacy groups brought suit against various brand name and generic drug manufacturers of the drug Cipro, alleging that the settlement agreement between the patent holder and the generic manufacturers violated antitrust laws.[7] The suit began when Barr, one of the generic manufacturers, filed an abbreviated new drug application (ANDA) seeking to market a generic version of Cipro, and contested the validity of Bayer's '444 patent.[8] Bayer, the brand name manufacturer, brought suit claiming patent infringement, and Bayer and Barr, as well as several other generic manufacturers, subsequently entered into settlement agreements.[9] The trial court held that the agreements did not violate the Sherman Act because the adverse effects on competition were within the patent's exclusionary zone, and therefore not subject to redress through antitrust law.[10]

The U.S. Court of Appeals for the Federal Circuit affirmed the trial court's grant of summary judgment to the defendants and Bayer's motion to dismiss.[11] In so holding, the court found that it was "well within" Bayer's rights to exclude the generic manufacturers from profiting off of sales of Cipro (or its generic counterpart), and the Sherman Act did not per se preclude the settlement of patent claims.[12] Citing *Valley Drug Co. v. Geneva Pharmaceuticals, Inc.*,[13] *In re Tamoxifen Citrate Antitrust Litigation*,[14] *Andrx Pharmaceuticals, Inc. v. Elan Corp.*,[15] and *Schering-Plough Corp. v. FTC*,[16] the court further held that where all anticompetitive effects of an agreement are within the exclusionary power of the patent holder, both patent law and antitrust law produce the same outcome: validity of the agreement unless it "restrict[s] competition beyond the exclusionary zone of the patent."[17]

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on certain payments received from the brand manufacturer. Therefore, because Hatch-Waxman provides 180 days' exclusivity for the first generic manufacturer to file an ANDA and challenge the brand manufacturer's patents, Pay for Delay can prevent other generic entry into the market.

[5]*See*, *e.g.*, Brief for the United States in Response to the Court's Invitation, *In re* Ciprofloxacin Hydrochloride Antitrust Litig., No. 05-cv-2851 (L) (2d Cir. July 6, 2009), *available at* http://www.justice.gov/atr/cases/f247700/247708.htm.

[6]544 F.3d 1323 (Fed. Cir. 2008).

[7]*Id.* at 1329.

[8]*Id.* at 1328.

[9]*Id.* The court notes, however, that "the [settlement] agreements were entered into before the 2003 amendments to the Hatch-Waxman Act, requiring a patent holder and a first Paragraph IV ANDA filer who settle their patent litigation to file their agreement with the [FTC] and Department of Justice for review." *Id.* at 1329 n.3 (citing Pub. L. No. 108-173, §1112; 21 U.S.C. §355(j)(5)(D)(i)(V)).

[10]*Id.* at 1330.

[11]*Id.* at 1327.

[12]*Id.* at 1333.

[13]344 F.3d 1294 (11th Cir. 2003).

[14]466 F.3d 187 (2d Cir. 2006).

[15]421 F.3d 1227 (11th Cir. 2005).

[16]402 F.3d 1056 (11th Cir. 2005).

[17]*In re Ciprofloxacin*, 544 F.3d at 1335–36*; see also In re Tamoxifen*, 466 F.3d 187.

The U.S. Court of Appeals for the Third Circuit addressed this issue in 2012. In *In re K-Dur Antitrust Litigation*,[18] the Third Circuit held that settlement agreements in which payments are made to the generic manufacturers challenging the patents to settle the litigation may be unreasonable restraints on trade and unenforceable under federal antitrust laws. In so holding, the Third Circuit adopted the "rule of reason" test, which requires the fact-finder to "treat any payment from a patent holder to a generic patent challenger who agrees to delay entry into the market as prima facie evidence of an unreasonable restraint of trade, which could be rebutted by showing that the payment (1) was for a purpose other than delayed entry or (2) offers some pro-competitive benefit."[19] The "rule of reason" test is in contrast to the "scope of the patent test," which has been used by the Second, Eleventh, and Federal Circuits and which concludes that such agreements do not violate the antitrust laws "so long as (1) the exclusion does not exceed the patent's scope, (2) the patent holder's claim of infringement was not objectively baseless, and (3) the patent was not procured by fraud on the [patent and trademark office]."[20] In another victory for the FTC, the Third Circuit also agreed with the FTC that the merits of the underlying patent suit need not be considered in the "rule of reason" test because the fact of settlement itself was evidence of a "reasonable litigation compromise."

On December 7, 2012, the U.S. Supreme Court granted certiorari in *Federal Trade Commission v. Watson Pharmaceuticals, Inc*.,[21] a case out of the Eleventh Circuit that directly confronts the issues raised by the Second, Eleventh, Federal, and Third Circuit Courts of Appeal. The specific question presented by the FTC is whether "pay for delay" contracts are ''per se lawful unless the underlying patent litigation was a sham or the patent was obtained by fraud (as the [Eleventh Circuit] held), or instead of presumptuously anti-competitive and unlawful (as the Third Circuit has held).''[22] The Court heard oral argument on the petition on March 25, 2013,[23] and on June 17, 2013, the Court issued its opinion in *FTC v. Actavis, Inc*.[24] In *Actavis, Inc*., the Court held that "pay for delay" contracts are not *per se* lawful and in some instances may violate antitrust laws.[25] Specifically, the Court held that:

> [A] reverse payment, where large and unjustified, can bring with it the risk of significant anticompetitive effects; one who makes such a payment may be unable to explain and to justify it; such a firm or individual may well possess market power derived from the patent; a court, by examining the size of the payment, may well be able to assess its likely anticompetitive effects along with its potential justifications

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[18]686 F.3d 197 (3d Cir. 2012).

[19]*Id*. at 218.

[20]*Id*. at 212–15.

[21]133 S. Ct. 787 (2012) (cert. granted).

[22]*Id*.

[23]To access all of the briefs and oral argument transcripts in *Federal Trade Commission v. Watson Pharmaceuticals, Inc*. (No. 12-416), visit the Court's Web site at http://www.scotusblog.com/case-files/cases/federal-trade-commission-v-watson-pharmaceuticals-inc/.

[24]133 S. Ct. 2223 (2013).

[25]*Id*. at 2227.

without litigating the validity of the patent; and parties may well find ways to settle patent disputes without the use of reverse payments.[26]

D. New Developments in the Scope of FDA Authority [New Topic]

The key statutory and regulatory developments affecting drug development and marketing during 2007 center on the Food and Drug Administration Amendments Act of 2007 (FDAAA),[27] taken together with the legislative, judicial, and scientific issues that are likely to have prompted its timely promulgation. Since the FDAAA's enactment and throughout 2010 and early 2011, the FDA took several steps to implement the FDAAA, including the promulgation of several regulatory guidance documents for the industry, litigation in key regulatory areas, and attempted imposition of liability for corporate executives and counsel. This section discusses the key developments in the scope of the FDA's authority under the FDAAA, and then details the FDA's recent efforts to implement the FDAAA's new provisions.

1. Kennedy-Enzi, the Enhancing Drug Safety and Innovation Act of 2006 [New Topic]

Kennedy-Enzi, the Enhancing Drug Safety and Innovation Act of 2006,[28] laid important groundwork for the FDAAA. The purpose of Kennedy-Enzi was "to amend the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act to improve drug safety and oversight."

Title I sought to amend the FDCA to require new drug and biologics sponsors to develop and comply with Risk Evaluation and Mitigation Strategies (REMS), in order to obtain and maintain FDA approval of such products. For REMS purposes, sponsors would be required to submit a pharmacovigilance statement, and associated justification, indicating whether (1) routine adverse-event reporting will be adequate to assess "serious risk" and to identify "unexpected serious risk" presented by the drug after approval, or (2) whether postmarketing studies or clinical trials are needed. With respect to any given drug, such postmarketing actions (or other REMS elements) would be required if the Secretary of Health and Human Services (HHS) makes the necessary determinations in each case.

Title IV of Kennedy-Enzi[29] amended the FDCA to add provisions governing the FDA's process for screening potential advisory committee members for conflicts of interest. In some cases the proposed new provisions differ from the requirements of 18 U.S.C. §208, the general statutory authority governing conflicts of interest for federal employees (including special government employees serving on advisory committees). This title would also require the FDA to disclose, before advisory committee meetings take place, specified information

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[26]*Id*. at 2237.

[27]Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823 (H.R. 3580). Section 901(d) of the FDAAA added §503B to the FDCA.

[28]Enhancing Drug Safety and Innovation Act of 2006, S. 3807, 109th Cong., Sec. 101, §505(o) (amending 21 U.S.C. §355).

[29]*Id.* tit. IV.

regarding conflicts of interest and FDA waivers allowing members to vote and/or participate in committee meetings.

2. The Food and Drug Administration Amendments Act of 2007 [New Topic]

On September 27, 2007, President George W. Bush signed into law the FDAAA, which amended the FDCA and the Public Health Service Act.

The FDAAA was enacted to "amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the postmarket authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes."[30] The FDAAA amended Section 505 of the FDCA[31] to improve the transparency of information about drugs and also to allow patients and health care providers to have better access to information about drugs.

The FDAAA is arguably the most important legislative development in U.S. food and drug law in decades. It addresses issues for which the FDA has been criticized: insufficient oversight and regulatory support. Although parts of the FDAAA extend and reaffirm previous programs with some modifications, other sections dramatically change the way the FDA regulates medical products. The Act provides the FDA with new resources to monitor the safety of drugs,[32] authorizes and empowers the FDA to compel manufacturers to make labeling changes,[33] and allows the FDA to require manufacturers to undertake postmarketing safety studies.[34]

The FDAAA is divided into Titles I–X, addressed below, and further into subtitles and sections.

a. Title I—Prescription Drug User Fee Amendments of 2007 and Title II—Medical Device User Fee Amendments of 2007 [New Topic]

Congress has been criticized for leaving the FDA with a multiplicity of unfunded mandates.[35] It remains unclear whether the new funding provisions in the FDAAA will be sufficient to allow the FDA to perform its existing and new legislative mandates.

The Prescription Drug User Fee Act of 1992 (PDUFA I) was passed by the House on October 6 and the Senate on October 7, and was signed into law on October 29, 1992.[36] PDUFA I amended the FDCA to authorize the FDA to collect user fees with respect to "human drug applications, prescription drug establishments, and prescription drug products" and thereby supplement the review activity resources of the FDA by making those additional funds available for the

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[30]Pub. L. No. 110-85, Preamble.

[31]21 U.S.C. §355.

[32]FDAAA, Pub. L. No. 110-85, tit. I, Sec.103(b)(4), §736(b), 121 Stat. 823, 828 (2007).

[33]FDAAA, tit. IX, §901(a), §505(o)(4), 121 Stat. at 924–26.

[34]*Id.* §505(o)(3), 121 Stat. at 923–24.

[35]Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 Admin. L. Rev. 431, 438 (2008); *see also* Charles Marwick, *FDA Funding Problems Imperil Safety of Biological Products in the United States*, 279 JAMA 899–901 (1998).

[36]Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (codified at 21 U.S.C. §§379g, 379h, amended by PDUFA II in 1997).

review of drug applications.[37] PDUFA was legislatively reauthorized in 1997 (PDUFA II)[38] and 2002 (PDUFA III).[39]

FDAAA extends and reaffirms PDUFA's targeted fiscal budgetary requirements. The FDAAA amended FDCA Chapter VII[40] by adding a new Section 736A,[41] empowering the FDA to collect fees ("to generate revenue amounts of $6,250,000 for each of fiscal years 2008 through 2012")[42] deemed necessary to fund oversight ("advisory review")[43] operations of Direct-to-Consumer (DTC)[44] advertisements.

The FDAAA imposes new sunset provisions, noting that the amendments made by Sections 102, 103, and 104 cease to be effective on October 1, 2012,[45] and the Reporting Requirements in Section 105 cease to be effective on January 31, 2013.[46]

In September 2011, the FDA also issued a guidance addressing requests for waivers, refunds, and reductions of user fees under Sections 735 and 736 of the FDCA.[47] The guidance describes the types of waivers and reductions, as well as the eligibility criteria and procedures for applying for a waiver or reduction. Waivers or reductions are available if necessary to protect the public health, if the assessment of the fee presents a significant barrier to innovation, or if the applicant is a small business submitting its first human drug application. Waivers or reductions may also be available if the fees imposed exceed the costs of conducting the human drug application process, although the guidance does not address that type of waiver. Several products are exempt from fees, including orphan-designated products, applications by state or federal agencies for drugs that are not distributed commercially, and applications or supplements withdrawn before any substantial work is performed on the application or supplement. Finally, the guidance describes the procedure for submitting requests for waivers, reductions, and refunds.[48]

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[37]21 U.S.C. §379(g) (2008) (note that PDUFA I was amended by PDUFA II).

[38]Pub. L. No. 105-115, 111 Stat. 2296 (1997).

[39]Pub. L. No. 107-188, 116 Stat. 613 (2002).

[40]21 U.S.C. §§379g *et seq.*

[41]*Id.* §379h-1.

[42]FDAAA, Pub. L. No. 110-85, tit. I, §104(b), 121 Stat. 823 (2007).

[43]"The term 'advisory review' means reviewing and providing advisory comments on DTC advertisements regarding compliance of a proposed advertisement with the requirements of this Act prior to its initial public dissemination." *See* FDAAA, tit. I, §104(h)(1), 121 Stat. 823.

[44]"The term 'direct-to-consumer television advertisement' means an advertisement for a prescription drug product (as defined in section 735(3)) intended to be displayed on any television channel for less than 3 minutes." *See* FDAAA, tit. I, §104(h)(4), 121 Stat. 823.

[45]*See* 21 U.S.C. §379g (Sec. 102, Definitions; Sec. 103, Authority to assess and use drug fees; and Sec. 104, Fees relating to advisory review of prescription-drug television advertising).

[46]*See id.* §379h-2 (Sec. 105, Reauthorization; reporting requirements).

[47]*See* U.S. Dep't Health & Human Servs., Food & Drug Admin., Guidance for the Public, User Fee Waivers, Reductions, and Refunds for Drug & Biological Products (Sept. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079298.pdf. The guidance details the FDA's current thinking on the scope of user fees under Sections 735 and 736, and revises a 1993 draft guidance.

[48]Requests for waivers or reductions—for application, product, or establishment fees—must be submitted no later than 180 calendar days after the fee is due, and may be submitted in advance to avoid having to pay the fee. The FDA recommends that advance requests be submitted three

On July 9, 2012, President Obama signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012,[49] which included the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA V),[50] new provisions for the new Generic Drug User Fee Amendments of 2012 (GDUFA),[51] and the Biosimilars User Fee Act of 2012 (BUFA).[52] GDUFA provides for (1) a one-time backlog fee, (2) a drug master file fee, (3) an ANDA and prior approval supplemental filing fee, and (4) a generic drug facility fee and an active pharmaceutical ingredient facility fee. The FDA's goal with the GDUFA is to enhance safety, access, and transparency of generic drugs. In August 2012, the FDA issued a Draft Guidance for Industry on the application of GDUFA.[53] The Draft Guidance clarified the FDA's current thinking on the application of GDUFA and details industry requirements for backlog fees, drug master file fees, ANDA and prior approval supplement fees, facility fees, and other fee-related issues.

Like the GDUFA, the BUFA would authorize the FDA to collect fees such as a (1) biosimilar development program fee, (2) annual biosimilar biological product application and supplement fee, (3) biosimilar biological product establishment fee, and (4) biosimilar biological product fee. The goal of the BUFA is to expedite the review process for biosimilar biological products.

b. Title III—Pediatric Medical Device Safety and Improvement Act of 2007 [New Topic]

The FDAAA statutorily creates the Pediatric Medical Device Safety and Improvement Act, which, for the first time, incentivizes device manufacturers to create products that specifically meet the needs of pediatric patients. Of note, the FDAAA empowers the FDA to waive pediatric testing requirements, stating that "if the course of the disease or condition and the effects of the device are sufficiently similar in adults and pediatric patients, the Secretary may conclude that adult data may be used to support a determination of a reasonable assurance of effectiveness in pediatric populations, as appropriate."[54]A similar provision applies to testing in pediatric subpopulations.[55]

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to four months before submission of the application or before the product and establishment fees are due. *Id.*

[49]Pub. L. No. 112–144 (July 9, 2012), 126 Stat. 993.

[50]U.S. Dep't of Health & Human Servs., Food & Drug Admin., PDUFA V: Fiscal Years 2013–2017, *available at* http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

[51]21 U.S.C. §379j-42.

[52]21 U.S.C. §379j-52.

[53]Food & Drug Admin., Dep't of Health & Human Servs., Guidance for Industry, Generic Drug User Fee Amendments of 2012: Questions and Answers (Aug. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM316671.pdf.

[54]FDAAA, Pub. L. No. 110-85, tit. III, §515(b)(1), 121 Stat. 823 (2007).

[55]*Id.* §515(b)(2).

c. Title IV—Pediatric Research Equity Act of 2007 and Title V—Best Pharmaceuticals for Children Act of 2007 [New Topic]

On December 2, 1998, the FDA originally promulgated the "Pediatric Rule," which asserted the FDA's authority to compel drug manufacturers to complete pediatric testing for pharmaceuticals.[56] The American Association of Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert subsequently litigated and successfully challenged the validity of the Pediatric Rule in the U.S. District Court for the District of Columbia.[57] The result was that in 2002 the Pediatric Rule was invalidated by the court's holding that the FDA lacked statutory authority to promulgate such a regulation.

The Best Pharmaceuticals for Children Act of 2002[58] (BPCA) and the Pediatric Research Equity Act of 2003[59] were designed to improve the quality and quantity of pharmaceuticals available to children, but included sunset provisions for 2007. The FDAAA reauthorizes both acts for an additional five years, with relatively minor changes.

The BPCA was passed to address the concern that, at that time, the majority of prescription medications were never tested in, and therefore not specifically approved for use in, children. The BPCA was passed after the Food and Drug Administration Modernization Act of 1997 (FDAMA)[60] and provided for pediatric exclusivity—six months of marketing exclusivity for pharmaceutical companies that conducted pediatric studies.[61] The FDAAA prohibits pharmaceutical manufacturers from filing late applications to the FDA for pediatric testing,[62] a practice that presumably had been engaged in with the intent of extending the life of the drug patent.

Moreover, the FDAAA empowers the HHS Secretary, after consultation with the sponsor, to issue to the sponsor or holder a written request for the con-

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[56]21 C.F.R. §§201, 312, 314, 601 (2001); 63 Fed. Reg. 66,632 (1998).

[57]Association of Am. Physicians & Surgeons, Inc. v. U.S. Food & Drug Admin., 226 F. Supp. 2d 204 (D.D.C. 2002) (the labeling provisions of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§321 *et seq.*, such as 21 U.S.C. §201(n), do not provide a clear basis for the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 21 C.F.R. §§201, 312, 314, 601).

[58]Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, 115 Stat. 1408 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

[59]Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

[60]Pub. L. No. 105-115, §111, 111 Stat. 2296 (1997) (codified as amended in scattered sections of 21 U.S.C.) (provisions expired in 2001).

[61]The term "pediatric studies" or "studies" means at least one clinical investigation (which, at the Secretary's discretion, may include pharmacokinetic studies) in pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary, may include preclinical studies. FDAAA, Pub. L. No. 110-85, tit. V, §505A(a), 121 Stat. 823 (2007); *see also id.* §505A(m)(1)–(2); U.S. Dep't Health & Human Servs., Food & Drug Admin., The Pediatric Exclusivity Provision: January 2001 Status Report to Congress (2001), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049915.pdf.

[62]"Exception–The Secretary shall not extend the period referred to in paragraph (1)(A) or (1)(B) if the determination made under subsection (d)(3) is made later than 9 months prior to the expiration of such period." FDAAA, tit. V, §505A(b)(2), 121 Stat. 823 (2007).

duct of pediatric studies for such drug.[63] Adverse-event reports by sponsors to the FDA are mandatory.[64]

The pediatric mandate in the FDAAA amends the Program for Pediatric Studies of Drugs[65] to read as follows:

> (a) List of Priority Issues in Pediatric Therapeutics.—
> (1) Not . . . later than one year after the date of the enactment of the Best Pharmaceuticals for Children Act of 2007, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs and experts in pediatric research, shall develop and publish a priority list of needs in pediatric therapeutics, including drugs or indications that require study. The list shall be revised every three years.[66]

The FDAAA reauthorizes the Pediatric Research Equity Act of 2007 (PREA 2007),[67] which extended the PREA of 2003 for an additional five years with some modifications. The PREA 2007 requires a pharmaceutical manufacturer to supply greater documentation in order to receive a pediatric testing waiver. In addition, the FDAAA empowers the FDA with broader authority to mandate pediatric testing.[68]

d. Title VI—Reagan-Udall Foundation [New Topic]

Title VI, Section 601 of the FDAAA amends Chapter VII of the FDCA[69] to establish the Reagan-Udall Foundation for the FDA. The foundation is to be a nonprofit corporation and explicitly shall "not be an agency or instrumentality of the United States Government."[70] The purpose of the foundation is "to advance the mission of the [FDA] to modernize medical, veterinary, food, food ingredient, and cosmetic product development, accelerate innovation, and enhance product safety."[71]

The duties of the foundation are enumerated broadly to include policy and program development and funding in the areas of safety, research, and education by doing the following:

> (1) taking into consideration the Critical Path reports and priorities published by the Food and Drug Administration, identify unmet needs in the development, manufacture, and evaluation of the safety and effectiveness, including postapproval, of devices, including diagnostics, biologics, and drugs, and the safety of food, food ingredients, and cosmetics, and including the incorporation of more sensitive and predictive tools and devices to measure safety;
> (2) establish goals and priorities in order to meet the unmet needs . . . ;
> (3) in consultation with the Secretary, identify existing and proposed Federal intramural and extramural research and development programs relating to the goals

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[63]*Id.* §505A(d)(1)(A).
[64]*Id.* §505A(d)(2)(B); *see also id.* §505A(d)(2)(l)(1).
[65]Public Health Service Act §409I (2007) (codified at 42 U.S.C. §284m).
[66]FDAAA, tit. V, §505A(q)(1)(B)(b), 121 Stat. 823 (2007).
[67]Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936, *amended as* Pediatric Research Equity Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended at 21 U.S.C. §301).
[68]*See* FDAAA, tit. V, §505A (Pediatric Studies of Drugs).
[69]21 U.S.C. §§371 *et seq.*
[70]FDAAA, tit. VI, §601(a).
[71]*Id.*

and priorities established under paragraph (2), coordinate Foundation activities with such programs, and minimize Foundation duplication of existing efforts;

(4) . . . award grants to, or enter into contracts, memoranda of understanding, or cooperative agreements with, scientists and entities, which may include the Food and Drug Administration, university consortia, public-private partnerships, institutions of higher education, entities described in section 501(c)(3) of the Internal Revenue Code . . . ;

(5) recruit meeting participants and hold or sponsor (in whole or in part) meetings as appropriate to further the goals and priorities established under paragraph (2);

(6) . . . release and publish information and data and, to the extent practicable, license, distribute, and release material, reagents, and techniques to maximize, promote, and coordinate the availability of such material, reagents, and techniques for use by the Food and Drug Administration, nonprofit organizations, and academic and industrial researchers to further the goals and priorities established under paragraph (2); . . . .[72]

Title VI, Section 602 of the FDAAA amends Chapter IX of the FDCA[73] by adding Section 910,[74] "thereby establishing the Office of the Chief Scientist, a person appointed by the Secretary." The duties of the Office include the mandate to

(1) oversee, coordinate, and ensure quality and regulatory focus of the intramural research programs of the Food and Drug Administration;

(2) track and, to the extent necessary, coordinate intramural research awards made by each center of the Administration or science-based office within the Office of the Commissioner, and ensure that there is no duplication of research efforts supported by the Reagan-Udall Foundation for the Food and Drug Administration;

(3) develop and advocate for a budget to support intramural research;

(4) develop a peer review process by which intramural research can be evaluated;

(5) identify and solicit intramural research proposals from across the Food and Drug Administration through an advisory board composed of employees of the Administration that shall include—

(A) representatives of each of the centers and the science-based offices within the Office of the Commissioner; and

(B) experts on trial design, epidemiology, demographics, pharmacovigilance, basic science, and public health; and

(6) develop postmarket safety performance measures that are as measurable and rigorous as the ones already developed for premarket review . . . .[75]

Title VI, Section 603 further amends Subchapter E of Chapter V of the FDCA[76] to empower the

> Secretary, acting through the Commissioner of Food and Drugs, [to] enter into collaborative agreements, to be known as Critical Path Public-Private Partnerships, with one or more eligible entities to implement the Critical Path Initiative of the Food and Drug Administration by developing innovative, collaborative projects in research, education, and outreach for the purpose of fostering medical product inno-

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[72]*See* FDAAA, tit. VI—Reagan-Udall Foundation. Chapter VII of the FDCA (21 U.S.C. §§371 *et seq.*) is amended by Subchapter I, §770 (21 U.S.C. §379dd) as §601(c).

[73]21 U.S.C. §§391 *et seq.*

[74]*Id.* §399a.

[75]FDAAA, Pub. L. No. 110-85, tit. VI, §602(b)(1)–(6), 121 Stat. 823 (2007).

[76]21 U.S.C. §§360bbb *et seq.*

vation, enabling the acceleration of medical product development, manufacturing, and translational therapeutics, and enhancing medical product safety.[77]

e. Title VII—Conflicts of Interest [New Topic]

The issue of bias[78] in drug development and pharmaceutical research continues to receive much attention in scientific and regulatory circles.[79] In 1989, researchers detecting possible scientific bias suggested that the FDA implement measures such as certifying the competence of potential investigators; providing for peer-reviewed, competitive application for the opportunity to conduct FDA-authorized clinical trials; limiting an investigator's level of participation in clinical trials; penalizing manufacturers who fail to detect their investigators' misconduct; and permitting the FDA to suspend investigators prior to a hearing.[80]

Subsequently, in January 2002, the FDA issued a Draft Guidance on Disclosure of Conflicts of Interest for Special Government Employees Participating in FDA Product Specific Advisory Committees, and requested comments on the draft guidance.[81] In the *Federal Register* on October 31, 2007, the FDA followed with a draft guidance consistent with the FDA's good guidance practices regulation[82] to represent the agency's views on the public availability of information regarding FDA advisory committee members' financial interests and waivers granted by the FDA to permit members' participation in advisory committee meetings.[83]

The FDA then developed a Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees, dated March 2007, which describes the factors and analyses to be used in the consideration of whether an advisory committee member has a potential conflict of interest and whether participation in a meeting is appropriate.[84] This draft guidance is issued consistent with the FDA's established good guidance practices regulation.[85]

Title VII of the FDAAA amends Subchapter A of Chapter VII of the FDCA[86] by inserting a legislative mandate requiring "disclosure of any finan-

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[77]FDAAA, tit. VI, §603(a), 121 Stat. 823.

[78]B.M. Psaty et al., *Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis*, 292 JAMA 2622–31 (2004).

[79]U.S. Dep't Health & Human Servs., Food & Drug Admin., Draft Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility in FDA Advisory Committees (Mar. 2007), *available at* http://www.fda.gov/oc/advisory/waiver/coiguidedft.html.

[80]M.F. Shapiro & R.P. Charrow, *The Role of Data Audits in Detecting Scientific Misconduct: Results of the FDA Program*, 261 JAMA 2505–11 (1989).

[81]71 Fed. Reg. 61,657 (Oct. 31, 2007).

[82]Codified at 21 C.F.R. §10.115.

[83]72 Fed. Reg. 61,658 (Oct. 31, 2007).

[84]72 Fed. Reg. 13,805 (Mar. 23, 2007), *available at* http://www.fda.gov/opacom/morechoices/industry/guidedc.htm.

[85]21 C.F.R. §10.115 (2008).

[86]21 U.S.C. §§371 *et seq.*; 21 U.S.C. §379d-1.

cial interest[87] prior to any meeting of an advisory committee regarding a particular matter (as that term is used in Section 208 of Title 18 of the U.S. Code), [and providing that] each member of the committee who is a full-time Government employee or special Government employee shall disclose to the Secretary financial interests."[88] Thereafter, the "member of an advisory committee may not participate with respect to a particular matter considered in an advisory committee meeting if such member (or an immediate family member of such member) has a financial interest that could be affected by the advice given to the Secretary with respect to such matter."[89] In keeping with the principle of transparency, the FDAAA mandates the Secretary to "ensure that the public record and transcript of each meeting of an advisory committee includes the [required] disclosure."[90]

f. Title VIII—Clinical Trial Databases [New Topic]

The American Medical Association (AMA) Council on Scientific Affairs approved a resolution in 2004 recommending the public registration of all clinical trials at inception, with the results from these trials to be made publicly available through either journal publication or an electronic data repository.[91] The Pharmaceutical Research and Manufacturers of America (PhRMA) Principles were revised in June 2004 to improve public access to drug trial data.[92] PhRMA has also established a centralized electronic database to facilitate the public's access to clinical trial data and the results of unpublished clinical studies.[93]

An Interagency Oncology Task Force (IOTF) was established in 2003 to increase the efficiency of clinical research and the scientific evaluation of new potential cancer-treating pharmaceuticals and diagnostic modalities. In September 2006, the HHS/FDA and the HHS/National Institutes of Health (NIH)/National Cancer Institute (NCI) jointly published a Memorandum of Understanding (MOU) to establish a formal collaboration designed to develop and implement the Federal Investigator Registry of Biomedical Information Research Data (FIREBIRD), a collaboration designed to enable clinical investigators, NCI, FDA, and industry entities sponsoring clinical trials of investigational drugs (Sponsors) to manage clinical investigator information electronically in a fully secure manner.[94] Information that is entered into FIREBIRD by a

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[87]The term "financial interest" is defined in the FDAAA to mean "a financial interest under section 208(a) of title 18, United States Code." FDAAA, Pub. L. No. 110-85, tit. VII, §712(a)(2), 121 Stat. 823 (2007) (conflicts of interest, amending 21 U.S.C. §379d-1).

[88]*Id.* §701(c)(1).

[89]*Id.* §701(c)(2)(A).

[90]*Id.* §701(d).

[91]*See Drug Controversies Prompt Call for Clinical Trial Registry*, Am. Med. Ass'n News (July 5, 2004), *available at* http://www.ama-assn.org/amednews/2004/07/05/hll20705.htm; *see also A.M.A. Adds Its Voice to Call for Disclosure on Drug Trials*, N.Y. Times (June 16, 2004), *available at* http://query.nytimes.com/gst/fullpage.html?res=9A02E3D81E30F935A25755C0A9629C8B63.

[92]PhRMA Principles (2004) (revised principles), *available at* http://www.phrma.org/publications/publications//2004-06-30.1035.pdf.

[93]PhRMA Clinical Study Results Database, *available at* http://www.clinicalstudyresults.org/.

[94]71 Fed. Reg. 54,285, 54,286 (Sept. 14, 2006).

Sponsor may become a matter of "FDA record" (a submission to FDA) only if the submitter takes an affirmative step acknowledging that the data are accessible by the FDA.

The MOU was codified in April 2007, under the designation Janus Study Data Repository.[95] The MOU notes that the

> FDA and NCI both have interests in expediting the development of new drugs. One of the central goals of the IOTF is to implement an electronic drug application submission system that will help reduce the delays, errors, and costs associated with drug development. Such a system is expected to speed the discovery and delivery of new therapies.[96]

The FDAAA requires an expanded clinical trial registry data bank intending to "enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials."[97] Moreover, the 2007 Amendments state that

> [N]ot later than 18 months after the date of the enactment of the [FDAAA], the Director of NIH shall ensure that the public may search the entries of the registry data bank by the safety issue, if any, being studied in the clinical trial as a primary or secondary outcome.[98]

g. Title IX—Enhanced Authorities Regarding Postmarket Safety of Drugs [New Topic]

The FDA is charged with the responsibility of ensuring the safety and effectiveness of drugs, biologics, and devices pursuant to the FDCA[99] and Section 351 of the Public Health Service Act.[100] Congress required that information regarding the safety of pharmaceuticals be reported to the FDA so that the agency can take appropriate action to protect the public health when necessary.[101] Congress authorized investigational powers to the FDA.[102] These statutory requirements and powers are duly codified in the *Code of Federal Regulations*.[103] Section 130(a) of the FDAMA[104] amended the FDCA by adding a provision requiring reports of postmarketing studies for approved human drugs and licensed biological products.[105] In order to determine whether drugs that are not

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[95]72 Fed. Reg. 19,534, 19,535 (Apr. 18, 2007).

[96]*Id.*

[97]FDAAA, Pub. L. No. 110-85, tit. VIII—Clinical Trial Databases, §801(a) (codified at 42 U.S.C. §282(j)(2)(A)(i)).

[98]*Id.*

[99]Sections 201, 502, 505, and 701 of the FDCA (21 U.S.C. §§321, 352, 355, and 371), require that marketed drugs be safe and effective. *See* 21 U.S.C. §§355, 360b, 360c, 360e, and 393 (2008).

[100]42 U.S.C. §262 (2008).

[101]*See* FDCA §§505(j) and 704 (21 U.S.C. §§355(j), 374).

[102]*See* FDCA §702 (21 U.S.C. §372).

[103]*See* 21 C.F.R. pts. 310 (New Drugs), 314 (Applications for FDA Approval to Market a New Drug), 600 (Biological Products: General), and 1271 (Human Cells, Tissues, and Cellular and Tissue-Based Products). Parts 310, 314, 600, and 1271 mandate the use of Form FDA 3500A for reporting to FDA adverse events that occur with drugs and biologics.

[104]Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (S. 830).

[105]21 U.S.C. §356b (2008) (stating in part, "A sponsor of a drug that has entered into an agreement with the Secretary to conduct a postmarketing study of a drug shall submit to the Secretary, within 1 year after the approval of such drug and annually thereafter until the study is

safe and effective are on the market, the FDA must be promptly informed of any potential adverse experiences related to the use of any marketed pharmaceuticals. Applicants who receive marketing approval of drug products are required to report to the FDA any serious, unexpected adverse drug experiences, and any necessary follow-up reports.[106] Manufacturers, packers, and distributors must maintain for 10 years records of all adverse drug experiences required to be reported.[107]

FDA approval of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) allows the sponsor to market that drug only for certain uses, treatments, and indications, all of which must be indicated on FDA-approved labeling.[108] Thus, FDA approval is conditional, and by statute the FDA can withdraw or suspend approval of a product at any time if new evidence reveals that the drug does not meet the safety or efficacy standards purported in the applications.[109] The FDA is informed of such "new evidence" in part by reports from sponsors and manufacturers of approved drugs, which must describe any reported adverse reactions to their products, and in part through postmarket surveillance studies (sometimes referred to as Phase IV studies).

In 2003,[110] the FDA had proposed to amend its pre- and postmarketing safety reporting regulations for human drug and biological products to implement definitions and reporting formats and standards recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and by the World Health Organization's Council for International Organizations of Medical Sciences. The rulemaking intended to codify FDA's expectations for timely submission, acquisition, and evaluation of relevant safety information relating to marketed drugs and licensed biological products. The FDA proposed to amend its postmarketing annual reporting regulations for human drug and licensed biological products to revise the content for these reports.[111]

With respect to pharmaceuticals, decisions regarding labeling requirements require the FDA to engage in a complex balancing of interests[112] between warnings that overstate or exaggerate risks, which may deter appropriate use, and labeling that understates risks or side effects, because both will adversely affect public health and safety.

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completed or terminated, a report of the progress of the study or the reasons for the failure of the sponsor to conduct the study.").

[106]*See* 21 C.F.R. §314.80(b) (2008) (stating in part, "Each applicant having an approved application under §314.50 or, in the case of a 505(b)(2) application, an effective approved application, shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.").

[107]21 C.F.R. §310.305(f) (2008).

[108]21 U.S.C. §355(b)(2) (2008); 21 C.F.R. §314.3 (2008).

[109]21 U.S.C. §355(e) (2008).

[110]68 Fed. Reg. 12,406 (Mar. 14, 2003).

[111]71 Fed. Reg. 6281, 6283 (Feb. 7, 2006).

[112]71 Fed. Reg. 3922, 3934 (Jan. 24, 2006).

The withdrawal of the drug Rofecoxib[113] in 2004, together with safety concerns associated with several other drugs,[114] raised questions about the integrity of the U.S. drug safety system.[115] In response, and at the request of the Center for Drug Evaluation and Research of the FDA,[116] the Institute of Medicine (IOM) issued a comprehensive review and set of recommendations for reforms.[117]

The FDAAA embodies provisions relating to Risk Evaluation and Mitigation Strategies (REMS) earlier proposed by the Kennedy-Enzi Enhancing Drug Safety and Innovation Act of 2006.[118] The FDA now has express authority[119] to impose REMS, which are mandatory plans intended to ensure that the benefits of a prescription drug or biologic outweigh that product's risks.[120]

Title IX, Section 901 of the FDAAA amends Section 505 of the FDCA.[121] The section on REMS amends Chapter V of the FDCA[122] by inserting after Section 505-1 authorization for the Secretary to consider the following factors at the time of initial approval of a new pharmaceutical:

(A) The estimated size of the population likely to use the drug involved.
(B) The seriousness of the disease or condition that is to be treated with the drug.
(C) The expected benefit of the drug with respect to such disease or condition.
(D) The expected or actual duration of treatment with the drug.
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
(F) Whether the drug is a new molecular entity.[123]

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[113]C.D. Furberg & B.M. Psaty, *COX-2 Inhibitors: Lessons in Drug Safety*, 352 N. Eng. J. Med. 1133–35 (2005).

[114]E.A. Gale, *Lessons from the Glitazones: A Story of Drug Development*, 357 Lancet 1870–75 (2001).

[115]P.B. Fontanarosa et al., *Postmarketing Surveillance: Lack of Vigilance*, *Lack of Trust* [editorial], 292 JAMA 2647–50 (2004).

[116]U.S. Government Accountability Office, Drug Safety: Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process, GAO-06-402 (Mar. 2006), *available at* http://www.gao.gov/new.items/d06402.pdf.

[117]Committee on the Assessment of the U.S. Drug Safety System, The Future of Drug Safety: Promoting and Protecting the Health of the Public (A. Baciu et al., eds., National Academies Press 2007); *see also* U.S. Dep't Health & Human Servs., Food & Drug Admin., The Future of Drug Safety: Promoting And Protecting the Health of the Public: FDA's Response to the Institute of Medicine's 2006 Report (Jan. 2007), *available at* http://www.fda.gov/oc/reports/iom013007.html.

[118]Enhancing Drug Safety and Innovation Act of 2006, S. 3807, 109th Cong., Sec. 101, §505(o) (amending 21 U.S.C. §355).

[119]73 Fed. Reg. 16,313 (Mar. 27, 2008) ("The [FDA] is issuing this notice to notify holders of certain prescription new drug and biological license applications that they will be deemed to have in effect an approved [REMS] under the [FDAAA]. Holders of applications deemed to have in effect an approved REMS are required to submit a proposed REMS to FDA.").

[120]Gerald F. Masoudi, *Legal Developments in the Enforcement of Food and Drug Law*, 63 Food & Drug L.J. 585, 586 (2008).

[121]21 U.S.C. §355.

[122]*Id.* §§351 *et seq.*

[123]FDAAA, Pub. L. No. 110-85, tit. IX, §901(b), 121 Stat. 823 (2007).

REMS also apply in the postapproval period requiring the Secretary, when he or she

> has approved a covered application . . . and did not when approving the application require a risk evaluation and mitigation strategy . . . [to, as needed,] subsequently require such a strategy for the drug involved (including when acting on a supplemental application seeking approval of a new indication for use of the drug) if the Secretary becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug.[124]

Section 901 of the FDAAA addresses postmarket safety for drugs and biologics. The FDAAA grants the FDA express authority to require additional postmarket testing.[125] Under these new provisions, the FDA may also order specific changes to the labeling for an approved drug based on new safety information and, as indicated, post new warnings. The agency is empowered to impose fines[126] if the sponsor fails to comply with agency requirements for further testing and warnings.[127] The pharmaceutical manufacturers will bear user fees that will fund the active surveillance system intended to delineate such postmarket drug risks.[128] Moreover, under the FDAAA, the agency has been granted the express authority to order such postmarket safety actions despite objections from the drug sponsor.

In April 2011, the FDA issued a guidance detailing the agency's current thinking on the implementation of Section 505(o)(3) of the FDCA, which authorizes the FDA to require postmarketing studies and clinical trials for prescription drugs approved under the FDCA and biological products approved under the Public Health Service Act, either at the time of approval or postapproval if the FDA becomes aware of new safety information.[129] According to the guidance, the FDA will require a postmarketing study or clinical trial when the decision to require such study or trial is based on appropriate scientific data and where adverse-event reporting (for postmarketing studies) or a postmarketing study (for clinical trials) would be insufficient to meet one of the purposes for either. Under Section 505(o)(3)(B), the purposes for a postmarketing study or clinical trial may be

(a) to assess a known serious risk related to the use of the drug;
(b) to assess signals of serious risk related to the use of the drug; or
(c) to identify an unexpected serious risk when available data indicate a potentially serious risk.

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[124]*Id.*
[125]*Id.* §901(a), 121 Stat. at 923.
[126]*Id.* sec. 902(b), §303(f), 121 Stat. at 943.
[127]*Id.*
[128]*Id.* sec. 905(a), §505(k), 121 Stat. at 944.
[129]*See* U.S. Dep't Health & Human Servs., Food & Drug Admin., Guidance for Industry, Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (Apr. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf. "New safety information" is defined to include information about a serious risk or unexpected serious risk associated with the use of the drug, or the effectiveness of the approved risk evaluation and mitigation strategy for the drug since the last assessment. *Id.*

If these conditions are met, a postmarketing study or clinical trial may be required, and the FDA may describe the study or trial, including how it will be conducted, the population, and the indication. Additionally, the FDA may require a postmarketing study or clinical trial if it becomes aware of a risk and believes it is serious, but requires additional knowledge to determine the appropriate response to the risk.[130] The guidance identifies the reporting requirements under Section 505(o)(3)[131] and explains that the failure to comply with the reporting requirements and other requirements of the law may result in enforcement action, unless the applicant can show good cause.

The FDA also issued a draft guidance detailing its current view on Section 505(o)(4) of the FDCA, which allows the FDA to require postapproval labeling changes to drug and biological-product labeling when the FDA has learned of new safety information.[132] The rule was enacted to modify the past practice of protracted labeling negotiations, which ultimately left the FDA with limited options if an application holder failed to comply. New safety information may be from "a clinical trial, an adverse event report, a postapproval study . . . [or] peer-reviewed biomedical literature, data derived from the postmarket risk identification and analysis system . . . or other scientific data deemed appropriate by [the Secretary]." As the draft guidance describes, when the FDA learns of the potential for new safety information, it will use a multidisciplinary team to review the information and determine whether a labeling change is necessary. The FDA anticipates that Section 505(o)(4) will be implemented when a change to the boxed warnings, contraindications, warnings and precautions, drug interactions, or adverse-reactions sections of the professional labeling is required. However, the FDA has indicated that if a change were warranted solely to the adverse-reactions section, the FDA would be unlikely to exercise its authority under Section 505(o)(4).

The FDA's use of Section 505(o)(4) may have one of several results: new labeling, an appeal of the FDA's order, or an enforcement action if the application holder does not comply. With regard to revised labeling, the FDA's guidance indicates that it should be available on the application holder's Web site within 10 calendar days of approval. As for the timing of implementing revised labeling

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[130]Applicants may appeal the imposition of a postmarketing study or clinical trial through the FDA's dispute resolution procedures. *Id.*; *see also* U.S. Dep't Health & Human Servs., Food & Drug Admin., Draft Guidance for Industry, Guidance for Industry Formal Dispute Resolution: Appeals Above the Division Level (Feb. 2000), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079743.pdf.

[131]An applicant is required to provide a timetable for completion of the postmarketing study or clinical trial, periodic reports on the status of the postmarketing study or clinical trial, and each postmarketing study or clinical trial that is "otherwise undertaken by the applicant to investigate a safety issue." Applicants may already be submitting such reports under existing regulations. *See* U.S. Dep't Health & Human Servs., Food & Drug Admin., Guidance for Industry, Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (Apr. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf.

[132]*See* U.S. Dep't Health & Human Servs., Food & Drug Admin., Draft Guidance for Industry, Safety Labeling Changes—Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (Apr. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf.

for package inserts and other printed materials, the FDA plans to issue a guidance on this topic. Alternatively, the FDA's guidance indicates that an appeals process is available for applicants who disagree with any ordered labeling changes. Should an application holder not comply with the FDA's order, the application holder may face an enforcement action by the FDA. This may include unapproved new drug charges, misbranding charges, civil monetary penalties, or seizure of the product and an injunction. Nonetheless, the FDA's guidance indicates a willingness to negotiate labeling changes using the platform provided by Section 505(o)(4).

The FDAAA defines an "adverse drug experience" to include "any adverse event associated with the use of a drug in humans, whether or not considered drug related," and including

(A) an adverse event occurring in the course of the use of the drug in professional practice;
(B) an adverse event occurring from an overdose of the drug, whether accidental or intentional;
(C) an adverse event occurring from abuse of the drug;
(D) an adverse event occurring from withdrawal of the drug; and
(E) any failure of expected pharmacological action of the drug.[133]

The Chief Counsel of the FDA has noted that "[t]he most far reaching and restrictive elements of a REMS are what FDAAA calls 'Evaluation of elements to assure safe use.'"[134] This section of the FDAAA describes many of the elements that sponsors have used in the past under the rubric of "restricted distribution plans." In order to impose elements to assure safe use, the FDA is required to first make a determination that the drug (1) is effective; (2) is associated with a "serious adverse drug experience," as that term is defined by the statute; and (3) can be approved only if elements to assure safe use are imposed.

To facilitate the tracking of adverse events, product problems, and medication/device use errors related to FDA-regulated products, two reporting forms are available: (1) FDA 3500, which is used for reporting by health care professionals and the public; and (2) FDA 3500A, which is designed for mandatory reporting by manufacturers and health care professionals reporting under the National Childhood Vaccine Injury Act of 1986.[135] The FDA has proposed modifications to Form FDA 3500 and Form FDA 3500A to better conform with current regulations, rules, and guidance documents; to better reflect the range of reportable products; to improve clarity; to better use available space for data entry; to offer voluntary reporters the opportunity to better characterize the sus-

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[133]FDAAA, Pub. L. No. 110-85, sec. 902(b), §303(f), 121 Stat. 823, 943 (2007).

[134]*See id.* tit. IX, §901(b), Postmarket Studies and Clinical Trials Regarding Human Drugs; Risk Evaluation and Mitigation Strategies.

[135]National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§300aa-1 to -34 (2008). Mandatory reports of untoward reactions to immunization are not submitted to FDA on either Form FDA 3500 or Form FDA 3500A, but are instead submitted to the joint FDA/Centers for Disease Control and Prevention Vaccines Adverse Event Reporting System (VAERS) on the VAERS-1 form, available at http://www.vaers.hhs.gov.

pected adverse event, product problem, or error; and to provide better-quality safety-related data for agency evaluation.[136]

The proposed extensions to Form FDA 3500 and Form FDA 3500A will have changes in the instructions to reflect the range of reportable products and provide clarity of reporting. Previous forms changes (2005–2008) allowed reporters to better use available space for data entry and offered voluntary reporters the opportunity to clearly describe the suspected adverse event, product problem, or error and provide better-quality safety-related data for agency evaluation.[137]

The FDA is also taking a more comprehensive approach to making information on potential drug risks available to the public. The FDA believes that timely communication of drug safety information best provides health care professionals, patients, consumers, and other interested persons access to the most current information concerning the potential risks and benefits of a marketed drug, helping them to make more informed individual treatment choices.[138] The heightened attention by the FDA to risk-communication efforts are considered to be an integral part of a larger drug safety initiative that dates back to November 2004.

FDAAA Section 917, entitled "Risk Communication," directs the Secretary to establish an Advisory Committee on Risk Communication. The drug safety program includes the following: (1) sponsoring an independent study by the Institute of Medicine of the National Academies of the effectiveness of the drug safety system, with emphasis on postmarketing risk assessment and surveillance; (2) conducting workshops and Advisory Committee meetings regarding complex drug safety and risk management issues, including emerging concerns; and (3) publishing three risk management guidances. In addition, the FDA augmented its drug safety initiative in February 2005 by creating an independent Drug Safety Oversight Board to enhance oversight of drug safety decision making within the Center for Drug Evaluation and Research (CDER).[139] In May 2005, the FDA issued a draft guidance titled FDA's Drug Watch for Emerging Drug Safety Information,[140] which described a proposal to establish a new communication channel, called the "Drug Watch" Web page, to provide information to the public on emerging drug safety issues. Given the similarity in names and the subsequent potential for confusion between the proposed "Drug Watch" and FDA's existing "MedWatch" programs, the FDA discontinued the name "Drug Watch" for the drug safety information Web page.[141]

Therefore, the FDAAA aims to enhance the information available to consumers about potential risks from advertised drugs and to prohibit the use of

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[136]70 Fed. Reg. 48,157, 48,158 (Aug. 16, 2005); *see* 73 Fed. Reg. 8879 (Feb. 15, 2008). These are now part of the MedWatch FDA Safety Information and Adverse Event Reporting Program, available at http://www.fda.gov/medwatch/safety/3500.pdf.

[137]73 Fed. Reg. 8879, 8880 (Feb. 15, 2008).

[138]72 Fed. Reg. 10,224 (Mar. 7, 2007).

[139]*Id.*

[140]70 Fed. Reg. 24,606 (May 10, 2005).

[141]The methods used to communicate important drug safety issues, including the mechanisms described in this guidance and the presentation of drug safety information, is posted on the FDA Web sites available at http://www.fda.gov and http://www.fda.gov/cder.

reminder advertisements to consumers. Disclosures by manufacturers must note on the FDA Web site (Safety Information Web Site) the limits on information regarding drug safety where agency approvals were based on surrogate endpoints during the clinical trials, evolving information obtained through postmarket studies or surveillance, and the significance of any failure to complete postmarket studies.[142]

The FDAAA comes at a time when the FDA has faced ever-increasing criticism regarding pharmaceuticals approved and then withdrawn from the market following safety concerns. Issues of inadequate funding and manpower, as well as research and administrative bias, have been raised. The FDAAA may thus represent an important legislative clarification of FDA authority and mandate, at least partially in an effort to decrease reliance on judicial interpretations.

3. The Patient Protection and Affordable Care Act [New Topic]

In 2010, the primary statutory and regulatory development affecting drug development and marketing was the Patient Protection and Affordable Care Act (PPACA),[143] along with several judicial advancements that may impact the scope of the FDA's oversight and regulatory authority.

On March 23, 2010, President Barack Obama signed into law PPACA, an act that represents one of the most comprehensive health care reform efforts since the creation of Medicare and Medicaid. PPACA was enacted in response to growing public concern regarding the disparities in the availability of health care and health care insurance, the rising cost of health care both in the public and private contexts, and the inequitable treatment of individuals covered by private health insurance. PPACA provides for incremental implementation of broad reforms ranging from the immediate creation of a national high-risk insurance pool, enhanced quality improvement measures, the restructuring of payment and eligibility for Medicare and Medicaid, and provisions addressing concerns about the health care work force, preventative medicine, tax changes, and employer participation.[144] The constitutionality of PPACA was challenged,[145] and on June 28, 2012, the U.S. Supreme Court issued a decision upholding the majority of the Act.[146]

a. Biologics Price Competition and Innovation Act of 2009 [New Topic]

The most significant expansion of FDA authority under PPACA was enacted through Title VII, specifically, the Biologics Price Competition and

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[142]FDAAA, Pub. L. No. 110-85, tit. IX, Sec. 915, §505, 121 Stat. 823, 957 (2007) (codified at 21 U.S.C. §355(r) (2008)).

[143]Patient Protection and Affordable Care Act (PPACA), Pub. L. No. 111-148, 124 Stat. 119 (2010) (H.R. 3590).

[144]Henry J. Kaiser Family Found., Focus on Health Reform: Health Reform Implementation Timeline 1–5 (June 15, 2010) [hereinafter Kaiser, Focus on Health Reform].

[145]For access to all materials submitted in the PPACA cases brought before the U.S. Supreme Court, including briefs and oral argument transcripts, see http://www.supremecourt.gov/docket/PPAACA.aspx.

[146]National Fed'n of Indep. Bus. v. Sebelius, 132 S. Ct. 2566 (2012).

Innovation Act of 2009 (BPCIA).[147] This provision gives the FDA authority "to approve generic versions of biologic drugs[,] grant biologics manufacturers 12 years of exclusive use before generics can be developed,"[148] and grant exclusivity rights to the first generic applicant that receives a determination of interchangeability status.[149]

In order to receive a determination of biosimilarity,[150] a generic drug's applicant must demonstrate five criteria: (1) the generic drug is biosimilar to the reference product,[151] (2) the generic drug and reference product[152] use the same mechanism(s) of action for the condition(s) of use prescribed, recommended, or suggested, (3) such condition(s) of use in the labeling of the generic drug have previously been approved for the reference product, (4) the route of administration, dosage, and strength of the generic drug are the same as the reference product's, and (5) the generic's manufacturing, processing, packing, or holding facility uses standards to assure the generic's retention of safety, purity, and potency.[153]

Similarly, a generic drug will be deemed interchangeable[154] if the product (1) is biosimilar to the reference product, (2) can be expected to produce the same clinical result, and (3) if intended for multiple administrations, has no greater risk of safety or diminished efficacy if used interchangeably with the reference product than the reference product would have without such interchangeability.[155]

The first drug application to receive a determination of interchangeability for a reference product will be granted exclusivity for a limited period.[156] Simi-

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[147]PPACA, §7002, 124 Stat. at 804.

[148]Kaiser, Focus on Health Reform, at 1.

[149]PPACA, §7002(a), 124 Stat. at 807.

[150]Biosimilar or biosimilarity means "(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." §7002(b), 124 Stat. at 815.

[151]The determination that a generic is biosimilar to the reference product must be supported with data derived from:

> (aa) analytical studies that demonstrate the [generic] is highly similar to the reference product[, excluding differences in clinically inactive components]; (bb) animal studies (including the assessment of toxicity); and (cc) clinical study[(ies)] . . . that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.

Id. §7002(a), 124 Stat. at 805.

[152]The term "reference product" refers to "the single biological product . . . against which a biological product is evaluated in an application submitted under" the BPCIA. *Id.* §7002(b), 124 Stat. at 815.

[153]*Id.* §7002(a), 124 Stat. at 805.

[154]Interchangeable or interchangeability "means that the biological product may be substituted for the reference product without the intervention of a health care provider who prescribed the reference product." *Id.* §7002(b), 124 Stat. at 815.

[155]*Id.* §7002(a), 124 Stat. at 806.

[156]That period of time will be defined:

> [U]pon the earlier of: (1) 1 year after the first commercial marketing of the interchangeable generic product, (2) 18 months after a final court decision on all patents in an action against the first generic applicant or the dismissal with or without prejudice of an action against the

larly, even though the BPCIA grants generic manufacturers the right to file an application for an interchangeable or biosimilar determination four years after the reference product is first licensed,[157] the reference product holds exclusivity for 12 years.[158]

Similar to existing regulations, the generic applicant must provide to the outside and in-house counsel of the reference product's sponsor information pertaining to the generic drug.[159] Moreover, the representative of the reference product's patent owner may also request disclosure of this information, as long as the representative notifies the reference product's sponsor and the generic applicant of its intent to maintain the requisite confidentiality of the applicant's information.[160]

On May 10, 2011, the FDA moved forward with implementation of the BPCIA through its proposed User Fee Program for Biosimilar and Interchangeable Biological Product Applications. Pursuant to its obligation under the BPCIA to consult with outside groups on user fee programs, the FDA sought comments in several areas of the BPCIA, including development and structure of the biosimilar user fee program, performance goals for the FDA's review of applications under the Act, and performance goals for applications for which the FDA is unable to grant approval due to exclusivity provisions of the BPCIA. Under the BPCIA, the FDA was required to submit the FDA's recommendations by January 15, 2012.[161] These recommendations eventually became the Biosimilars User Fee Act of 2012, which was enacted on July 9, 2012 as part of the PDUFA V reauthorization.[162]

As further implementation of the BPCIA, the FDA has issued four draft guidances on biosimilar product development that addressed (1) Questions and

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first generic applicant, (3) 42 months after approval of the generic as interchangeable if the applicant has been sued on the application and the litigation is pending, or (4) 18 months after approval of the generic as interchangeable if the generic has not been sued under (l)(6). *Id.* §7002(a), 124 Stat. at 807. Section (l)(6) of §7002 allows the patent owner of a reference product to file suit against the generic applicant for patent infringement within 30 days of the mutual exchange of patent lists or mutual agreement on patents. *Id.* §7002(a), 124 Stat. at 812–13.

[157]*Id.* §7002(a), 124 Stat. at 807.

[158]*Id.* Market exclusivity for new biological products and already marketed biological products may also be extended to 12 years and six months if the HHS Secretary determines that it requires information on the use of the reference product in the pediatric population. *Id.* §7002(g), 124 Stat. at 820. Similarly, the exclusivity period for a new or already marketed biological product licensed under Section 526 of the FDCA for use in a rare disease or condition is extended to seven years and six months if the HHS Secretary determines that it may be useful for pediatric populations. *Id.*

[159]*Id.* §7002(a), 124 Stat. at 809. The applicant must disclose the following information within 20 days after the generic's application has been accepted for review: (1) a copy of the application and information that describes the process(es) used to manufacture the generic drug, and (2) any other information requested by the reference product's sponsor. *Id.*

[160]*Id.*

[161]*See also* Vicki G. Norton & Lewis F. Gould, *Alert: FDA Proposes Pre-marketing User Fees for Biosimilar Product Manufacturers Comparable to Fees for Branded Manufacturers* (Duane Morris May 11, 2011), *available at* http://www.duanemorris.com/alerts/FDA_biologics_price_competition_innovation_act_user_fee_biosimilar_biological_4073.html.

[162]21 U.S.C. §379j-52.

Answers Regarding Implementation of the BPCIA,[163] (2) Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,[164] (3) Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product,[165] and (4) Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants.[166] The first guidance addresses public questions in the areas of biosimilarity or interchangeability, determining when a "biological product" is subject to a Biologics License Application (BLA) or NDA, and exclusivity. The second guidance, Scientific Considerations, reflects the FDA's current plan to implement a *totality-of-the-evidence* approach to reviewing biosimilar applications under the BPCIA, recommends that sponsors use a stepwise approach to demonstrate biosimilarity, and provides general scientific principles to use in conducting studies. The third guidance related to Quality Considerations details the FDA's advice to applicants on the specific factors used in assessing a biological product's biosimilarity. Finally, the fourth guidance was designed to create a unified approach to all formal meetings between sponsors or applicants and the FDA for biosimilar biological product development programs, as well as to assist sponsors or applicants in generating and submitting a meeting request to the FDA for biosimilar biological products.

b. Labeling Changes [New Topic]

PPACA amends Section 505(j) of the Federal Food, Drug, and Cosmetic Act[167] pertaining to ANDA, by expanding eligibility for approval even if the proposed label of the drug differs from the listed drug.[168] The drug on which the ANDA application was filed will no longer be considered misbranded if the label differs due to a labeling revision in Section (i) of the Act, the ANDA is otherwise eligible for approval,[169] the labeling revision does not include a change to the "warnings" section, and the application sponsor agrees to submit revised labeling of the drug.[170] This exception may be inapplicable, however, if the HHS

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[163]U.S. Dep't Health & Human Servs., Food & Drug Admin., Draft Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Feb. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf.

[164]U.S. Dep't Health & Human Servs., Food & Drug Admin., Draft Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Feb. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.

[165]U.S. Dep't Health & Human Servs., Food & Drug Admin., Draft Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf.

[166]U.S. Dep't Health & Human Servs., Food & Drug Admin., Guidance for Industry Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (Mar. 2013), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf.

[167]PPACA, Pub. L. No. 111-148, tit. X, §10609, 124 Stat. 119, 1014 (2010).

[168]*Id.* §10609, 124 Stat. at 1014–15.

[169]Eligibility for approval is subject to the expiration of a patent, exclusivity period, or delay in approval in §(5)(B)(iii) of the amended provision and the HHS Secretary's approval, within 60 days of expiration, of the revision to the labeling of the drug. *Id.* §10609, 124 Stat. at 1014.

[170]*Id.* §10609, 124 Stat. at 1014–15.

Secretary determines that such labeling has an adverse impact on safe uses of the drug. In that event, the ANDA application will not retain eligibility for approval if it does not implement revised labeling.[171] On February 12, 2013, the Office of Generic Drugs/Office of Pharmaceutical Science issued a policy addressing how the Office of Generic Drugs (OGD) should implement section 505(j)(10) of the Federal Food, Drug, and Cosmetic Act (OGD Policy).[172] The OGD Policy states that the FDA may approve an ANDA, even though certain changes have been made to the labeling for the reference listed drug (RLD), if: (1) "the approval of the RLD's labeling revision is made within 60 days before the expiration of a listed patent, an exclusivity period, or a 30-month stay delaying ANDA approval"; (2) "the approved revision to the labeling of the RLD does not include a change to the "Warnings" section"; and (3) "the FDA has determined that the continued presence of the labeling in effect before the revision will not adversely impact the safe use of the drug product."[173]

c. Expansions to FDA Interaction With the Pharmaceutical Industry [New Topic]

i. The Office of Women's Health [New Topic]

Though PPACA specifically provides that Section 3509, which in part creates the Office of Women's Health (Office), does not establish or modify any new regulatory authority,[174] the additional oversight created by this section mandates a review because pharmaceutical and biologics manufacturers may find themselves interacting with this office.

PPACA Section 3509 authorizes the Commissioner of Food and Drugs (Commissioner) to appoint a Director to the Office, and the Office will report to the Commissioner.[175] In relevant part, the Office will be responsible for establishing short- and long-term goals for issues concerning women's health. A part of this responsibility requires the Office to consult with pharmaceutical and biologics manufacturers on policies regarding women's health.[176] Accordingly, pharmaceutical or biologics manufacturers involved in drugs or biologics for women's health issues will find additional opportunities to direct and participate in the ongoing development of applicable products, and may see increased FDA inquiry or oversight of existing programming geared toward women's health.

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[171]*Id.* §10609, 124 Stat. at 1015.

[172]U.S. Dep't of Health & Human Servs., Office of Generic Drugs/Office of Pharmaceutical Science, *Generic Drug Labeling Revisions Covered Under Section 505(j)(10) of the Federal Food, Drug, and Cosmetic Act* (Feb. 12, 2013), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM339381.pdf.

[173]*Id*. at 11.

[174]PPACA tit. III, §3509(h), 124 Stat. at 537.

[175]*Id.* §3509(g), 124 Stat. at 536.

[176]*Id.* §3509(g), 124 Stat. at 536–37.

ii. The Cures Acceleration Network [New Topic]

PPACA additionally established the Cures Acceleration Network (CAN) in an effort to facilitate the development of high need cures.[177] Although the CAN will operate under the authority of the National Institutes of Health,[178] as a member of the board of this network, the FDA will play a pivotal role in guiding the development of high need cures.[179] The purposes of the CAN are to

(1) conduct and support revolutionary advances in basic research, translating scientific discoveries from bench to bedside;
(2) award grants and contracts to eligible entities to accelerate the development of high need cures;
(3) provide the resources necessary for government agencies, independent investigators, research organizations, biotechnology companies, academic research institutions, and other entities to develop high need cures;
(4) reduce the barriers between laboratory discoveries and clinical trials for new therapies; and
(5) facilitate review in the Food and Drug Administration for the high need cures funded by the [CAN] . . . .[180]

Among other institutions, both pharmaceutical companies and biotechnology companies are eligible entities to receive grants under the CAN.[181] In conjunction with the CAN and the FDA, pharmaceutical companies awarded grants will promote technologies supporting advanced research, development, and production of high need cures.[182] Grant recipients will also receive assistance from the CAN in the areas of establishing FDA and other regulatory compliant protocols for the development, manufacturing, review, approval, and safety surveillance of the high need cure.[183] The CAN focus for fiscal year 2013 is rescuing and repurposing drugs, tissue chip for drug screening, and identifying and validating drug targets.[184]

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[177]A "high need cure" is:

> [A] drug (as that term is defined by section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act), biological product (as that term is defined by section 262(i)), or device (as that term is defined by section 201(h) of the Federal Food, Drug, and Cosmetic Act) that, in the determination of the Director of NIH—
>
> (A) is a priority to diagnose, mitigate, prevent, or treat harm from any disease or condition; and
>
> (B) for which the incentives of the commercial market are unlikely to result in its adequate or timely development.

Id. tit. X, §10409(d), 124 Stat. at 978–79.

[178]*Id.* §10409(d), 124 Stat. at 979.

[179]In addition to sending a representative to serve on the board of the CAN, the FDA may participate in regular and ongoing communication with the entities engaged in research, and will provide approval for such activities. *Id.* §10409(d), 124 Stat. at 979–81.

[180]*Id.* §10409(d), 124 Stat. at 979.

[181]*Id.* §10409(d), 124 Stat. at 982.

[182]The development of high need cures will include "the development of medical products, behavioral therapies, and biomarkers that demonstrate the safety or effectiveness of medical products." *Id.*

[183]*Id.*

[184]U.S. Dep't Health & Human Servs., Nat'l Ctr. Advancing Translational Scis., Cures Acceleration Network, *available at* http://www.ncats.nih.gov/funding-and-notices/can/can.html.

4. The FDA and International Oversight [New Topic]

In an effort to improve the safety of imported food and medical products, the FDA has established overseas offices that will ensure raw material manufacturers' compliance with Good Manufacturing Practices (GMP). As of March 2010, the FDA had established a presence in China, India, Africa, Asia, Latin America, Europe, the Middle East, New Zealand, Canada, and Australia.[185]

The goals of the FDA's presence will be to increase understanding of overseas manufacturing processes for products destined for the United States, to collaborate with local authorities on compliance issues, and to perform inspections of manufacturing and processing facilities.[186] The ultimate responsibility for assuring compliance with the FDCA, however, still remains with the entity distributing the product, whether food, a pharmaceutical, or a medical device. This duality of responsibilities may result in overseas supply disruptions due to heightened FDA enforcement activity.

5. FDA Oversight of Compounding Pharmacies [New Topic]

The FDA has attempted to extend its oversight of compounding pharmacies by bringing, for example, a criminal prosecution against a former owner of a compounding pharmacy located in Colorado in *United States v. Bader*.[187] In an effort to define the scope of the FDA's authority, several briefings in the case revolved around the definition of "compounding" in federal and state laws.[188]

In *Bader*, the government sought to prosecute Thomas Bader for filling prescriptions and distributing human growth hormone (HGH). Pursuant to several provisions of the U.S. Code,[189] Bader was charged with conspiracy to facilitate the sale of smuggled goods, smuggling foreign manufactured HGH, mail fraud, and distributing HGH.[190] Crucial to the court's determination was the proper definition of "compounding," for as the court noted, "the FDA rigorously regulates the importation and distribution of finished drugs that are ready for distribution to consumers, but exercises relatively little regulatory oversight over the importation of drug ingredients to be used by pharmacists

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[185]Food & Drug Admin., FDA's International Posts: Improving the Safety of Imported Food and Medical Products (Mar. 2010), *available at* http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM187246.pdf.

[186]*Id.*

[187]*See* United States v. Bader, No. 1:07-cv-00338-MSK, 2009 WL 2219258 (D. Colo. July 23, 2009).

[188]*See*, *e.g.*, Opinion and Order Granting in Part, Motion for Judgment of Acquittal and Denying Remaining Motions, United States v. Bader, No. 1:07-cv-00338-MSK (D. Colo. Apr. 29, 2010); United States v. Bader, No. 1:07-cv-00338-MSK, 2009 WL 2219258, *1–3 (D. Colo. July 23, 2009).

[189]For example, 18 U.S.C. §371 ("conspiracy to facilitate the sale of smuggled goods"); 18 U.S.C. §371 ("the 'smuggled goods' being foreign-manufactured HGH"); 18 U.S.C. §1341 ("mail fraud . . . , in that he made various false representations and omitted material information to patients about the HGH he was supplying them"); 21 U.S.C. §333(e) ("distribution of HGH"). *Bader*, 2009 WL 2219258, at *1.

[190]*Bader*, 2009 WL 2219258, at *1.

to create 'compounded' drugs and over the distribution of such 'compounded' drugs to consumers."[191]

Bader and his associates had been allowed to import HGH as a result of their statements to the FDA, in which they indicated that the "HGH was being imported for use as an 'active pharmaceutical ingredient' ("API") for use in drug compounding, rather than being a finished drug."[192] Ultimately, upon receipt of a prescription for HGH, Bader would measure the HGH and inspect it for potency, measure the appropriate amount of saline solution to administer the HGH, and package both products for the consumer.[193]

The district court ultimately determined that the FDA did have the authority to regulate compounding pharmacies and to criminally prosecute violations of those policies.[194] This authority is predicated on several compliance policy guides promulgated post-*Western States*, which suggested the FDA's intent to regulate compounding pharmacies in certain circumstances.[195] The Colorado jury eventually convicted Bader of violations of the FDA based on the theories promulgated by the FDA,[196] but the decision was appealed.

In 2011, the U.S. Court of Appeals for the Fifth Circuit held in *Medical Center Pharmacy v. Holder*[197] that the "waiver" doctrine precluded the FDA from arguing its right to conduct limited inspections of compounding pharmacies. In *Medical Center Pharmacy*, 10 pharmacies that compounded prescription

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[191]*Id.*

[192]*Id.* at *2.

[193]*Id.*

[194]The court used the definition of "compounding" codified by Colorado statute on the basis that "[t]he FDA's longstanding policy of deferring to state regulation of compounded drugs . . . strongly suggests that state law is the appropriate place to look for a legal definition of the term compounding." Similarly, the court noted that drugs that are "compounded under state law . . . may be regulated if they fall within one or more of the criteria set forth in the [FDA policies]." *Id.* at *11.

[195]According to the court, the 2002 policy guides published after *Western States* indicated that "the FDA will continue [to] defer to state regulation of the traditional practice of compounding, but . . . 'when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer,' the FDA will consider taking regulatory action." *Id.* at *6. See also Section IV.D. in the main volume, nn.885–86 (discussing *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002) and noting that "Section 503A of the FDAMA of 1997 exempted compounded drugs from the standard drug approval requirements of the FDA, provided that the providers of compounded medications refrain from advertising or promoting particular drugs").

The *Bader* court further noted several of the factors used by the FDA in determining whether it could assert regulatory authority over a compounding pharmacy, including:

(i) that the drugs were compounded in significant amounts before a prescription was received;

(ii) the APIs used in the compounding were not from FDA-registered suppliers;

(iii) the products were being distributed to third parties for resale to customers, rather than to customers themselves; and

(iv) the compounded products were essentially copies of commercially available products.

Bader, 2009 WL 2219258, at *4.

[196]*See* Press Release, U.S. Dep't of Justice, *Former Colorado Springs Pharmacist Sentenced for Importation and Distribution of Chinese-Made Human Growth Hormones and Conspiracy to Distribute Anabolic Steroids* (June 10, 2010), *available at* http://www.fda.gov/ICECI/CriminalInvestigations/ucm215255.htm?sms_ss=email (noting 40-month sentence and conviction "for the importation and distribution of Chinese-manufactured human growth hormone and conspiracy to distribute anabolic steroids").

[197]634 F.3d 830 (5th Cir. 2011).

drugs filed suit challenging the FDA's authority to regulate compounded drugs. The district court granted summary judgment in favor of the pharmacies, holding that the compounded drugs were not "new drugs" and the pharmacies were exempt from the FDA's inspection authority pursuant to 21 U.S.C. §374(a)(2)(A). The FDA appealed, and the Fifth Circuit reversed and remanded. On remand, the district court reversed its original decision, ruling that the FDA had authority to conduct limited inspections of pharmacy records notwithstanding §374(a)(2)(A). The pharmacies appealed.

On this second appeal, the Fifth Circuit held that the FDA had forfeited the issue of its inspection authority when it failed to raise the objection in the first appeal. Further, the Fifth Circuit held that the district court's original inspection ruling—that "state-law-compliant pharmacies are exempt from FDA records inspections under 21 U.S.C. §374(a)(2)(A)"—was not plainly erroneous, even in light of the Fifth Circuit's first ruling that compounded drugs were "new drugs."

Courts continue to foreclose the FDA's attempts to expand its enforcement authority over compounding pharmacies. For example, the U.S. District Court for the Middle District of Florida in *United States v. Franck's Lab, Inc.*[198] denied a request by the FDA for an injunction and summary judgment against a compounding pharmacy, Franck's, and firmly rejected the FDA's contention that it had per se authority to regulate pharmacies compounding drugs for animal use.

Franck's is a national pharmacy chain based in Florida that distributes and compounds drugs for both animal and human use. The *Franck's* case began when, in 2004 and 2005, the FDA inspected compounding facilities owned by Paul Franck—Franck's CEO, owner, and a duly licensed Florida pharmacist. The FDA had concerns that Franck's was impermissibly manufacturing drugs; compounding drugs outside a valid veterinarian-client-patient relationship; and compounding drugs when approved drugs were otherwise available. After Franck's initial response to this inquiry, the FDA did not approach Franck's until 2009, when Franck's was investigated and reprimanded by the Florida Board of Pharmacy for a misfilled prescription. This incident prompted the FDA to reinspect Franck's facilities and issue an FDA Form 483. Then, in April 2010, the FDA sought a preliminary injunction to enjoin Franck's from distributing animal drugs compounded from bulk substances, asserting that it was a per se violation of the federal FDCA to compound animal medications from bulk substances. In contrast, Florida law permits pharmacists to compound animal medications from bulk substances, as do the laws in many other states.

In this significant decision, the district court denied the FDA's request for a preliminary injunction and summary judgment, concluding that the FDCA did not "give the FDA *per se* authority to enjoin the long-standing, widespread, state-regulated practice of pharmacists filling a veterinarian's prescription for a nonfood-producing animal by compounding from bulk substances."[199] In so holding, the court relied on several key factors that belied the FDA's assertion of authority over Franck's compounding activities. First, the court noted that although the literal language of the FDCA's new drug provisions might be "suf-

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[198]No. 5:10-cv-00147 (M.D. Fla. Sept. 12, 2011).

[199]*Id.*, slip op. at 79–80.

ficiently capacious" to grant authority over compounding and pharmacists, there was no language to indicate Congress's intent to impose the new drug-approval requirements on pharmacies compounding animal drugs—in fact, the legislative history demonstrated that manufacturers were the target of those requirements. Additionally, the court found that the FDA had the authority to draw a regulatory line between traditional compounding pharmacies and manufacturers, but had failed to exercise it. Thus, the court disagreed with the FDA's assertion that its "judicious exercise of its enforcement discretion" was sufficient to delineate authorized and unauthorized compounding activities, finding that the "first-of-its-kind enforcement action" in *Franck's* was plainly an improper basis to expand statutory authority. The court found the impropriety of this "enforcement discretion" to be exacerbated by the fact that violations of the FDCA could carry stiff criminal sanctions, and that "arbitrary enforcement [would therefore be] antithetical to our system of criminal justice."[200]

Although *Franck's*[201] was vacated on appeal for procedural reasons, its discussion still remains relevant as the FDA continues to works toward additional authority in the area of compounding pharmacies. The most significant recent expansion to the FDA's authority to regulate new drugs is in the area of compounding pharmacies. While compounding pharmacies have traditionally been regulated by state boards of pharmacy, a widely publicized fungal meningitis outbreak in October 2012 has led the FDA to refocus its attention on regulating compounding pharmacies. The fungal meningitis outbreak was traced by the Centers for Disease Control to epidural steroid injections compounded and packaged at the New England Compounding Center (NECC).[202] The FDA issued an FDA Form 483 to the NECC,[203] the NECC voluntarily recalled certain of its products, and the FDA commenced a national debate concerning the need for additional federal oversight of compounding manufacturers.[204]

The debates concerning the FDA's authority over compounding pharmacies culminated in the passage of the Drug Quality and Security Act on November 18, 2013 (DQSA).[205] As of November 2013, the DQSA was on its way to President Obama for signature. The DQSA establishes three primary changes to the FDA's authority over compounding legislation. First, the Act creates a new regulated entity, outsourcing facilities, that are permitted to engage in large scale pharmacy compounding without a patient-specific prescription. Second, the Act resurrects Section 503A of the Food Drug and Cosmetic Act (FDCA), which details the requirements that must be met for traditional compounding pharmacies to remain exempt from the FDCA's new drug, adequate use for labeling,

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[200]*Id.*, slip op. at 78.

[201]United States v. Franck's Lab Inc., Case No. 11-15350, Dkt. No. 6692502-2 (11th Cir. Oct. 18, 2012).

[202] Centers for Disease Control, CDC Responds to Multistate Outbreak of Fungal Meningitis and Other Infections, *available at* http://www.cdc.gov/hai/outbreaks/currentsituation/.

[203]Dep't Health & Human Servs., Food & Drug Admin, FDA Form 483 Issued to New England Compounding Pharmacy Inc. (Oct. 26, 2012), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM325980.pdf.

[204]New England Compounding Center, *available at* http://www.neccrx.com.

[205]H.R. 3204, 113TH CONG. (2013), Pub. L. No. 113-54 (signed Nov. 27, 2013), *available at* http://www.gpo.gov/fdsys/pkg/BILLS-113hr3204pcs/pdf/BILLS-113hr3204pcs.pdf.

and cGMP requirements. Third, the Act establishes new criminal penalties for several categories of conduct prohibited under the Act including reselling compounded drugs that are labeled "not for resale;" intentionally falsifying a prescription for a compounded drug; failing to report drugs or adverse events for an outsourcing facility; and, using advertisements or promotions of compounded drugs that are false or misleading in any particular.

6. Regulation of OTC Drugs and OTC Measuring Devices [New Topic]

The FDA has a well-established history of regulating over-the-counter (OTC) drugs through both an OTC drug monograph system and an OTC new drug application process. In September 2011, the FDA enhanced that regulation by releasing a Guidance on Time and Extent Applications for Nonprescription Drug Products.[206] The guidance describes the FDA's latest thinking on the information applicants should provide when requesting that conditions be added to the FDA's OTC drug monograph system. Specifically, the guidance focuses on the time-and-extent application (TEA) component of the monograph application process, which requires applicants to demonstrate that the condition has been marketed OTC to a material extent and for a material time. The guidance applies to any OTC drug that does not have any marketing experience in the United States or that was initially marketed in the United States after May 11, 1972, when the OTC drug review started.

As the first of two steps in the OTC drug monograph system inclusion process, the TEA must include information about the OTC condition. For example, this would include

- the intended OTC uses, strengths, or dosage forms;
- a list of all countries in which the condition has been marketed; and
- information on the marketing activities in those countries, including demographics, dosage-unit sales history, and the country's system for identifying adverse drug experiences.

The TEA applicant also needs to include English versions of the product labels from every country in which the condition is marketed. Applicants submitting a TEA for an OTC drug marketed for more than five years under an FDA-approved application are exempt from some of these requirements.

Additionally, in early 2011, the FDA also took steps to address several of its concerns regarding the labeling of OTC measuring devices. In May 2011, the FDA released a Final Guidance relating to over-the-counter liquid drug products that are sold with measuring devices such as spoons, cups, or droppers. Prompted by reports of accidental overdoses due to poorly labeled measuring devices, the FDA's guidance provides several nonbinding recommendations for OTC measuring devices, including that a liquid formulation should include a dosage delivery device that is calibrated with the same units as specified on the package and uses the same abbreviations, eliminating the use of zeros after decimal points

[206]U.S. Dep't Health & Human Servs., Food & Drug Admin., Guidance for Industry, Time and Extent Applications for Nonprescription Drug Products (Sept. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078902.pdf.

but ensuring the use of zeros before decimal points, avoiding extra markings on delivery devices, and performing usability studies of measuring devices. As the guidance makes clear, failure to issue proper labeling on the dosage delivery device may constitute misbranding and subject the manufacturer to liability under Section 502 of the FDCA.[207]

7. Corporate Executive and Attorney Liability Under FDA Regulations [New Topic]

Corporate liability, either for pharmaceutical corporate executives or attorneys, is an increasingly important issue for entities in the pharmaceutical industry to understand. This need has recently been heightened due to enforcement, regulatory, and judicial efforts defining the FDA's authority to prosecute infringements of its authorizing statutes and regulations. Most significantly, the FDA recently set forth, in its *Regulatory Procedures Manual* for FDA personnel, criteria for when it would refer a matter for potential prosecution under the *Park* doctrine.[208] In essence, the *Park* doctrine provides for criminal liability (first-time misdemeanor and possible subsequent felony) under the FDCA without proof that a corporate official acted with intent or even negligence. Thus, in the *Regulatory Procedures Manual*, the FDA stated it would consider several factors in determining if prosecution is warranted, including the corporate official's knowledge of an actual participation in the violation, whether the violation involves actual or potential harm to the public, whether the violation is obvious, whether the violation reflects a pattern of illegal behavior and/or failure to heed prior warnings, whether the violation is widespread, whether the violation is serious, the quality of the legal and factual support for the proposed prosecution, and whether the prosecution is a prudent use of FDA resources.[209]

Unfortunately, these criteria provide little additional guidance as to when the FDA will refer a matter for *Park* doctrine prosecution. That being said, responsible corporate officials at companies with a history of violations (evidenced by receiving Form FDA 483s and warning letters) or with violations that pose potential or actual harm to the public may be at particular risk for a *Park* doctrine referral.

Also, in 2011, the U.S. Supreme Court decided *Astra USA*, *Inc. v. Santa Clara County*.[210] In a unanimous decision, the Court determined that 340B entities, including public hospitals and community health centers that provide health services to the poor, could not sue pharmaceutical manufacturers for failing to comply with the Pharmaceutical Pricing Agreement (PPA) that the manufacturers entered into with the Health Resources and Services Administration (HRSA),

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[207]*See* U.S. Dep't Health & Human Servs., Food & Drug Admin., Draft Guidance for Industry, Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products (May 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM188992.pdf.

[208]United States v. Park, 421 U.S. 658 (1975).

[209]*See* U.S. Dep't Health & Human Servs., Food & Drug Admin., Regulatory Procedures Manual, §6-5, *available at* http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176738.htm.

[210]131 S. Ct. 1342 (2011). Justice Kagan took no part in the consideration or decision of the case.

a unit of HHS. The 340B program provides that covered entities are to be charged no more than the predetermined ceiling price derived from the "average" and "best" prices and rebates calculated under the Medicaid Drug Rebate Program. If a manufacturer overcharges a covered entity, HRSA may require the manufacturer to reimburse the covered entity.

In *Astra USA*, *Inc*., Santa Clara County, an operator of several 340B entities, sued Astra and eight other pharmaceutical manufacturers, alleged third-party beneficiaries, claiming that the companies overcharged 340B health care facilities in violation of the PPAs that the companies signed. The Court determined that "the absence of a private right to enforce the statutory ceiling price obligations would be rendered meaningless if 340B entities could overcome the obstacle by suing to enforce the contract's ceiling price obligations instead. The statutory and contractual obligations, in short, are one and the same."[211] The Court rejected Santa Clara County's contention that allowing a private enforcement of the contractual rights under the PPA would not undermine Congress's contemplated intent of "centralized enforcement in the government."[212] Finally, the Court ruled that HRSA and HHS were best suited, rather than the courts, for dealing with the whole picture related to Medicaid reimbursement.[213] The Court, however, took no position on how this ruling might affect the average wholesale price litigation currently pending in numerous jurisdictions. Nonetheless, this ruling is significant for pharmaceutical manufacturers for two reasons: it affirms the federal government's authority to prosecute alleged violations of PPAs, yet it also eliminates a potentially cumbersome avenue of liability by 340B entities.

In another 2011 case, *United States v. Stevens*,[214] the FDA attempted to hold GlaxoSmithKline's in-house counsel Lauren Stevens liable for alleged obstruction of justice and falsification of documents requested by the FDA in order to ascertain whether GlaxoSmithKline was marketing one of its products for an unapproved use. The FDA alleged that Stevens had withheld certain documents from the FDA and made misrepresentations in correspondence regarding GlaxoSmithKline's marketing activities. On May 10, 2011, the U.S. District Court for the District of Maryland granted Stevens's motion for judgment as a matter of law, finding that no reasonable jury could convict her of the alleged crimes.[215] The court relied in part on the improper discovery of attorney-client confidential documents, which the government had obtained through use of the crime-fraud exception to the attorney-client privilege. Further, the court found that the privileged documents demonstrated that Stevens had provided a thoughtful analysis of the broad documentation requested by the FDA. Finally, the court found that although some of the statements made in Stevens's correspondence were "not literally true," they were clearly made in good faith where Stevens relied on the advice of counsel and, therefore, she could not be

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[211]*Id*. at 1348.

[212]*Id*. at 1349.

[213]*Id*. at 1350.

[214]United States v. Stevens, RWT-10-694 (D. Md. May 10, 2011) (transcript of record), *available at* http://lawprofessors.typepad.com/files/110510stevens.pdf.

[215]*Id.* at 8.

held liable.[216] This decision is an important one for corporate attorneys of pharmaceutical companies and demonstrates that attorneys may have legal protection against unfounded claims by the FDA or over-burdensome discovery requests of privileged documents.

8. The Future of FDA Regulatory Authority [New Topic]

The FDA issued its strategic priorities for the years 2011–2015, detailing the focus of its regulatory efforts and future regulatory goals.[217] First, the FDA described its guiding principles for regulatory efforts including science-based decision making, innovation and collaboration, transparency, and accountability. With these guiding principles in mind, the FDA's cross-cutting strategic priorities include advancing regulatory science and innovation, strengthening the safety and integrity of the global supply chain, strengthening compliance and enforcement activities to support public health, expanding efforts to meet the needs of special populations, and advancing medical countermeasures and emergency preparedness. From a long-term perspective, the FDA plans to advance food safety and nutrition; promote public health by advancing the safety and effectiveness of medical products; establish an effective tobacco regulation, prevention, and control program; and manage organizational excellence and accountability. As these priorities make clear, the FDA anticipates that its regulatory role will continue to expand.

Additionally, as part of its 2006 Unapproved Drug Initiative, in March 2011 the FDA announced its intention to take additional "enforcement action against unapproved and misbranded oral drug products [labeled for] prescription use and offered for relief of symptoms of cold, cough, or allergy and persons who manufacture or cause the manufacture of such products."[218] Prior to this initiative, a company could market an unapproved drug if the drug product predated legislation requiring evidence of safety and effectiveness. Affected companies were ordered to stop manufacturing the drugs by June 1, 2011, and to stop shipping the unapproved products by August 30, 2011. Enforcement actions included the removal of more than 500 medications falling into three categories: products in extended-release form, products containing active ingredients in tannate salt form (e.g., phenylephrine tannate), and certain immediate-release products. The FDA specifically removed these products due to their belief that some drugs were inappropriately labeled for use in infants and children, some products were manufactured incorrectly and could lead to inappropriately large or ineffective dosages, and some products had potentially risky combinations of ingredients. It is apparent from this enforcement effort that the FDA may continue in these

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[216]*Id.* at 7.

[217]*See* U.S. Dep't Health & Human Servs., Food & Drug Admin., Strategic Priorities 2011–2015, *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM252092.pdf.

[218]Drugs for Human Use; Unapproved and Misbranded Oral Drugs Labeled for Prescription Use and Offered for Relief of Symptoms of Cold, Cough, or Allergy; Enforcement Action Dates, 76 Fed. Reg. 11,794 (Mar. 3, 2011), *available at* http://www.gpo.gov/fdsys/pkg/FR-2011-03-03/pdf/2011-4703.pdf.

efforts: in a written statement the FDA expressed its concern regarding the undisclosed status of the products and unknowing prescriptions by providers.

In a further effort to increase its authority over the drug and biologic industries, on February 27, 2012, the FDA issued a draft guidance[219] encouraging manufacturers of prescription drug and biologic products to voluntarily notify FDA of issues that may result in a shortage of the product in the U.S. market or potential disruption in the supply. The FDA identified potential issues that may lead to a shortage or disruption, including

- product quality problems;
- interruptions or adjustments in manufacturing;
- delays in acquiring critical raw materials or components;
- transfer of manufacturing to an alternative facility;
- loss of production line or production capacity;
- production problems that occur during or after manufacturing that can result in supply disruptions;
- import delays;
- unexpected increases in demand; and
- product discontinuances.

Together, these various measures demonstrate the FDA's continued interest in asserting an increasingly broad presence in many areas related to pharmaceuticals.

IV. Marketing and Advertising Issues for Pharmaceutical Research

A. Basic Product Labeling Requirements

Additionally, in March 2013, the FDA issued a guidance[220] for sponsors of new drug applications (NDAs and ANDAs) that provides criteria for evaluating and labeling tablets that have been scored. The FDA considers tablet scoring when determining whether a generic drug product is the same as the reference listed drug (RLD). Patients often use scoring to facilitate the splitting of a tablet into fractions when less than a full tablet is the desired dose. The Drug Safety Oversight Board of the Center for Drug Evaluation and Research (CDER) considered the practice of tablet-splitting, and the FDA conducted internal research on splitting. The FDA then issued the guidance, with guidelines and criteria to help ensure safety and effectiveness in drug products that are scored and subsequently split. The guidance includes requirements that the dosage amount after splitting not be below the minimum therapeutic dose on the approved labeling,

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[219]Draft Guidance for Industry on Notification to Food and Drug Administration of Issues That May Result in a Prescription Drug Shortage; Availability, 77 Fed. Reg. 11,550 (Feb. 27, 2012), *available at* http://www.gpo.gov/fdsys/pkg/FR-2012-02-27/pdf/2012-4439.pdf.

[220]U.S. Dep't Health & Human Servs., Food & Drug Admin., Guidance for Industry on Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation (Mar. 2013), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269921.pdf.

that the split tablet should be safe to handle, and that the split tablet should maintain adequate stability, to name a few. The guidance also contains recommendations regarding post-splitting safety and modified release products, and it recommends that scoring for generic products be the same as for RLDs. Finally, the guidance includes criteria for the label and labeling.

B. Regulation of Direct-to-Consumer Advertising

[*Editor's Note*: The following paragraph should be inserted after the paragraph ending with footnote 790 in Section IV.B. in the main volume.]

In the future, the FDA may also require prescription drug promotional labeling or print advertising to include a quantitative summary, in a standardized format, of the risks and benefits of prescription drugs. As mandated by PPACA, the Commissioner of Food and Drugs must submit a report to the HHS Secretary determining the impact of such quantitative summaries on health care decision making by clinicians, patients, and consumers.[221] If the Commissioner finds that such dissemination will positively impact such decision making, the FDA will be required to promulgate associated regulations within three years of the report submission.[222] The First Progress Report under this section was submitted to Congress on March 23, 2011,[223] concluding that existing literature provided an insufficient basis to determine the impact of quantitative summaries. As a result, the First Progress Report recommended that the conducting of additional studies, a literature review, and consultation are necessary prior to the promulgation of regulations. In 2012, a final technical report on the presentation of quantitative benefit information in DTC television and print advertisements for prescription drugs was completed,[224] and a literature review of communicating quantitative risks and benefits in promotional prescription drug labeling or print advertising was accepted on January 10, 2013.[225] The final technical report generally concludes that "inclusion of quantitative benefit information in DTC print and television ads has the potential to help people make informed decisions about speaking with their health care professional about prescription drugs."[226]

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[221]PPACA, Pub. L. No. 111-148, tit. III, §3507(a), 124 Stat. 119, 530 (2010).

[222]*Id.* §3507(d), 124 Stat. at 530.

[223]U.S. Dep't Health & Human Servs., Food & Drug Admin., Report to Congress—Implementation of Section 3507 of the Patient Protection and Affordable Care Act of 2010, First Progress Report (Mar. 23, 2011), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM250581.pdf.

[224]U.S. Dep't Health & Human Servs., Food & Drug Admin., Ctr. for Drug Evaluation & Research, Office of Medical Policy, Presentation of Quantitative Benefit Information in Direct-to-Consumer (DTC) Television and Print Advertisements for Prescription Drugs: A Randomized Study (2012), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM343804.pdf.

[225]RTI Int'l (for the U.S. Dep't Health & Human Servs., Food & Drug Admin.), *Communicating quantitative risks and benefits in promotional prescription drug labeling or print advertising* (Jan. 10, 2013), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM343806.pdf.

[226]U.S. Dep't Health & Human Servs., Food & Drug Admin., Ctr. for Drug Evaluation & Research, Office of Medical Policy, Presentation of Quantitative Benefit Information in Direct-to-Consumer (DTC) Television and Print Advertisements for Prescription Drugs: A Randomized

[Note: the remainder of this chapter has been omitted from this extract.]