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The Office of Combination Products: Its Roots, Its Creation, and Its Role

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This paper is submitted in satisfaction of both the course requirement and the third-year written work requirement.

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Abstract

The Office of Combination Products (OCP), within the Food and Drug Administration (FDA), was created formally by statute in December, 2002. Upon its creation, the Office became broadly responsible for overseeing the regulation of combination products, or products that involve components that would normally be regulated under different FDA Centers. But the statutory creation of this Office in one day represented the culmination of nearly sixty-five years of both technological advancement in the products submitted to the FDA and amassed experience within the FDA and its administrative predecessors for managing those products in the name of the public safety. To understand the need for this Office and its primary goals of timely, effective and clear regulation of these groundbreaking technologies, the history of the FDA with respect to the advent of these combination products must be examined chronologically. Drafts of statutes, administrative proposals offered for public comment, and lengthy debates from Capitol Hill all illustrate the journey that led inevitably to the OCP as a final destination. Nearly twenty-four months have passed since the OCP was created, so an analysis of its initial progress through an explanation of the changes it has effected is necessary. Both combination product manufacturers and FDA jurisdiction officers have benefited from industry guidances, enhanced inter-Center communication, and a wealth of expertise provided by FDA employees eager to streamline the regulatory pathways to be navigated. Thus, the next three years within the OCP would seem to promise similar success for product manufacturers, the FDA and the American public.

Introduction

The [Office of Combination Products] “is a significant step to increase the efficiency and timeliness of the procedures that make these important products available to patients. I also believe that the activities of this new office will help provide insights into how the Commissioner’s office can better support a range of issues that cut across the three product centers, and thus bring greater uniformity and coherence to our processes.”¹

Mark B. McClellan, M.D., Ph.D., Commissioner of Food and Drugs.

By 2002, the Food and Drug Administration (FDA) had spent nearly two decades attempting to regulate in an orderly and thorough manner those new products that seemed to be more than just a new drug or a new biological product, or simply a medical device, but rather a combination of more than one of those categories. The Medical Device User Fee and Modernization Act (MDUFMA), signed into law on October 26, 2002 by President George W. Bush,² explicitly called for a formalization of that regulation. Among the other amendments that MDUFMA made to the statutory framework of the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA), the organic statute of the FDA, it required the FDA to establish an Office of Combination Products within sixty days “to ensure the prompt assignment of combination products to agency centers, the timely and effective premarket review of such products, and consistent and appropriate postmarket regulation of like products subject to the same statutory requirements to the extent permitted by law.”³ On December 31, 2002, FDA Commissioner Mark McClellan notified the American public that this Office had indeed been created and that, as a new part of the Office of the Commissioner, its responsibilities would include the regulation of the entire “life cycle of combination products, including jurisdiction decisions as well as the timeliness and effectiveness of pre-market review, and the consistency and appropriateness of

²Medical Device User Fee and Modernization Act of 2002 (hereinafter “MDUFMA”), Pub. L. No. 107-250, 21 U.S.C. § 301 *et seq.* (2002); President’s Statement on Signing the Medical Device User Fee and Modernization Act of 2002, 38 WEEKLY COMP. PRES. DOC. 1874 (November 4, 2002).

³MDUFMA § 204(3), 21 U.S.C. § 353 (2004). Interestingly, the President’s statement, *supra* note 2, made no mention of the new Office or its role.

post-market regulation.”⁴

Nearly twenty-four months later, this Office of Combination Products (OCP) has survived public hearings and opportunities for comment regarding its structure and regulatory policies, as well as its first mandatory Annual Report to Congress.⁵ In addition, it has promulgated multiple regulations to manage its Congressional responsibilities.⁶ Thus, the time is right to undertake a critical review of the initial steps taken by the FDA to institute the OCP. The goal of this paper is to elucidate the current structure of the OCP by examining the chain of historical developments that ultimately required its creation.

Section I introduces the pertinent provisions of the FDCA⁷ and traces the statutory development of how the FDA has defined a drug, a medical device, and a biological product since the inception of the FDCA. Armed with those definitions, Section I then traces the regulatory procedures for each of those three product categories to illustrate the diversity of approval procedures that exist within the FDA. This illustration throws into relief the long-felt need for the OCP to coordinate the regulation of products that implicate more than one product category. Section II details the historical and noteworthy developments surrounding the initial appearance of and subsequent increase in combination products during the latter half of the 20th Century. This chronological treatment highlights the gradual change in the FDA’s sophistication towards the regulation of this new product category. Section III explores the legislative history surrounding the passage of the Safe Medical Devices Act (SMDA) of 1990, and the provision that led to numerous changes in the way the

⁴See *supra* n.1.

⁵Office of Combination Products Annual Report to Congress (October 26, 2003), available at <http://www.fda.gov/oc/combination/Congressreport.pdf> (last visited April 16, 2004).

⁶See 21 C.F.R. §§ 3.1-3.7, 5.7 (2004).

⁷Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 321 *et seq.* (1938).

FDA regulates thousands of products each year. Section IV explains the contribution of the Food and Drug Administration Modernization Act (FDAMA) of 1997 to the regulation of combination products. Section V describes the latest and most dramatic changes accompanying the regulation of combination products: the Medical Device User Fee and Modernization Act (MDUFMA) of 2002. From this Act, the OCP was born. Section VI examines the current status of the OCP and Section VII concludes the analysis.

I. Basic Definitions and Regulatory Procedures for Drugs, Medical Devices, and Biologics

The FDCA was first enacted in 1938 as a measure to protect the health and safety of the American public through the uniform federal regulation of food, drugs, medical devices and cosmetics. The FDA, while existing in a variety of forms and under different monikers within multiple federal departments since 1862⁸, was statutorily recognized in 1988.⁹ Now a division of the Department of Health and Human Services, the FDA is responsible for executing and enforcing the FDCA¹⁰ and portions of the Public Health Service Act.¹¹ Most drugs (for human or animal use), medical devices, and biological products introduced into American interstate commerce must first survive a lengthy approval process overseen by the FDA.¹² Any food, drug, medical device, cosmetic or biological product that is adulterated or misbranded potentially subjects the manufacturer, shipper, and seller of that product to a variety of civil and criminal penalties.¹³

⁸ See Peter Barton Hutt, *A Historical Introduction*, 45 FDC L.J. 17 (1990).

⁹ 102 Stat. 3048, 3120-22 (1988).

¹⁰ 21 C.F.R. § 5.10(a)(1) (2004).

¹¹ Public Health Service Act, 42 U.S.C. § 201 (2004).

¹² 21 U.S.C. §§ 355, 360b, 360e (2004); 42 U.S.C. § 262(a) (2004).

¹³ See 21 U.S.C. §§ 342-43, 351-52, 361-62 (2004); 42 U.S.C. § 262 (2004). Violations of the FDCA and the accompanying penalties are codified at 21 U.S.C. §§ 331-37 (2004).

The choice of the FDA to prosecute a violation of the FDCA is usually reviewed only to ensure that the choice was not “arbitrary or capricious,”¹⁴ and the selective nonenforcement of the FDCA by the FDA is nearly unreviewable.¹⁵

I. A. Drugs

Pursuant to the FDCA, a “drug” is any article, or component thereof, “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man” or “intended to affect the structure or any function of the body of man.”¹⁶ Drugs were originally defined in 1938 to exclude devices, but the Safe Medical Devices Act of 1990 (SMDA) eliminated that exclusion.¹⁷ Other than the single amendment in 1990, the definition of a “drug” has remained the same since 1938.

The regulation of premarket approval and postmarket surveillance of FDA-approved drugs rests with the Center for Drug Evaluation and Research (CDER).¹⁸ A portion of the FDA staff has been devoted to studying and approving new drugs since the enactment of the FDCA in 1938.¹⁹ The current form of CDER, however, is the result of multiple institutional changes within the FDA. The Center for Biologics Evaluation and Research (CBER) was transferred from the National Institutes of Health (NIH) to the FDA in 1972

¹⁴See Administrative Procedure Act, 5 U.S.C. § 706(2)(A) (2004).

¹⁵See *Heckler v. Chaney*, 470 U.S. 821 (1985).

¹⁶21 U.S.C. §§ 321(g)(1)(B)-(C), (g)(2) (1938).

¹⁷21 U.S.C. § 321(g)(1), amended by Safe Medical Devices Act of 1990, Pub. L. No. 101-629, sec. 16(b)(1), 104 Stat. 4511 (November 28, 1990); see *infra* Section I.B.

¹⁸See 21 C.F.R. §§ 314 et seq., 21 C.F.R. § 5.701(a)(3) (2004).

¹⁹See Donna Hamilton, *Brief History of CDER*, at <http://www.fda.gov/cder/about/history/Histext.htm> (last visited April 16, 2004).

while it still bore the name of the Bureau of Biologics.²⁰ At this time, CDER was actually titled the Bureau of Drugs. In 1982, the two Bureaus were united within the FDA to form the National Center for Drugs and Biologics, later renamed the Center for Drugs and Biologics.²¹ Their union was formal, not functional. The union, moreover, was temporary; the two groups were divided in 1988 when the Center for Drugs and Biologics was split into CDER and CBER.²² CBER now oversees the premarket approval of biologics, as discussed *infra* at Section I.C. CDER is the largest Center within the FDA, boasting over one thousand employees, eleven major Offices and seven subsidiary Divisions.²³ Just recently, CBER and CDER partially reunited once again. The latest division of CBER's jurisdiction was finalized in late 2004 into a CBER-only review regime and a review regime under CDER. CDER now bears the responsibility for the review of therapeutic biologics (excepting cell and gene therapy products and therapeutic vaccines) that traditionally were reviewed only by CBER.²⁴

Currently, the role of CDER is divided among four major activities: new drug development and review, generic drug review, over-the-counter drug review, and post drug approval activities.²⁵ The approval of a new drug is the most scientifically rigorous, time-consuming and expensive process that CDER, and the FDA, undertakes. A drug manufacturer, or sponsor, who wishes to have a new drug marketed within the United States, must file an Investigational New Drug Application (IND) with CDER.²⁶ The IND contains animal pharmacology and toxicology data that (hopefully) demonstrates that the drug will be initially safe

²⁰ See PETER BARTON HUTT & RICHARD A. MERRILL, FOOD AND DRUG LAW 664 (2d ed. Foundation Press 1991) (hereinafter "HUTT & MERRILL").

²¹ *Id.*

²² *Id.* See *supra* n.19. See also 53 Fed. Reg. 8978 (March 18, 1988).

²³ See *supra* n.19; U.S. Food and Drug Administration, Center for Drug Evaluation and Research, CDER Offices and Divisions Page, at <http://www.fda.gov/cder/office.htm> (last visited April 16, 2004).

²⁴ 68 Fed. Reg. 38067, 38068 (June 26, 2003). See also CBER Transfer of Therapeutic Products to CDER, at <http://www.fda.gov/cber/transfer/transfer.htm> (last visited April 16, 2004). See, e.g. CBER Annual Report FY 2003, at <http://www.fda.gov/cber/inside/annrpt.htm> (last visited February 3, 2005).

²⁵ CDER Handbook, at <http://www.fda.gov/cder/handbook> (last visited April 16, 2004).

²⁶ *Id.*; Investigational New Drug Application, at <http://www.fda.gov/cder/handbook/index.htm> (last visited April 16, 2004). See 21 C.F.R. §§ 314.1 et seq.

in humans, and proposed clinical trial and manufacturing information. If CDER approves the IND, the sponsor may proceed with clinical trials using humans and ship the drug in interstate commerce as part of those clinical trials.²⁷ At the close of the clinical trials, the sponsor may file a New Drug Application (NDA) with CDER.²⁸ The sponsor must show, through clinical data resulting from two human trials, that the drug is both safe and effective for human use.²⁹ In addition, the sponsor must now contribute a user fee to accompany the NDA and any later application supplements in exchange for CDER's review of the NDA.³⁰

The sponsor of a new generic, or "me-too"³¹ version, of a "pioneer" drug that already has premarket approval from CDER does not need to file a full NDA. Rather, those "me-too" drugs are permitted to pursue an abbreviated NDA approval (ANDA)³² once the patent and period of market exclusivity for the "pioneer" drug has expired.³³ Approval of an ANDA prior to marketing of the "me-too" drug simply requires evidence of the drug's bioequivalence to the "pioneer" drug.³⁴ Once a drug has been approved by CDER, ongoing postmarket surveillance of the drug takes place, with input from the medical profession, the pharmaceutical industry, the World Health Organization, other federal agencies (both foreign and domestic), and cooperative agreements with drug safety evaluation databases.³⁵

²⁷*Id.*

²⁸*See* 21 U.S.C. § 355 (1938); *see also* Kefauver-Harris Amendments, Pub. L. No. 87-781, 76 Stat. 780 (October 10, 1962).

²⁹21 U.S.C. § 321(p) (2004); 21 U.S.C. § 355(d)-(e); 21 C.F.R. § 314.50, 34 Fed. Reg. 14596 (September 19, 1969).

³⁰21 U.S.C. § 379j(a) (2004); FDA Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296, sec. 103 (November 21, 1997).

³¹*See* HUTT & MERRILL at 478.

³²21 U.S.C. § 355(j).

³³*Id.* at § 355(j)(2)(A)(vii).

³⁴*Id.* at § 355(j)(2)(A)(iv).

³⁵Drug Experience/Epidemiologic Sources Available to FDA (for Post-Marketing Surveillance and Risk Assessment), at <http://www.fda.gov/cder/handbook/index.htm> (last visited April 16, 2004).

I. B. Medical Devices

Medical devices were also subject to the original FDCA as it was enacted in 1938. A “device” included

“instruments, apparatus, and contrivances, including their components, parts, and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals.”³⁶

In 1976, Congress amended the FDCA through the passage of the Medical Device Amendments.³⁷ The definition of a “device” was altered in part to reflect the increasing sophistication that the FDA witnessed in the design and capability of proposed medical devices. A “device” was more broadly defined to include an “implement,” “machine,” “implant,” “*in vitro* reagent, or other similar or related article.”³⁸ More importantly, the broadened definition of a “device” modified the language “intended to affect the structure or any function of the body of man.” To eliminate overlap in the regulation of drugs, biologics, and devices, Congress used the 1976 Amendments to require that a device “not achieve any of its principal intended purposes through chemical action within or on the body...” nor be “dependent upon being metabolized for the achievement of any of its principal intended purposes.”³⁹

Devices were classified under the 1976 Amendments to belong to one of three classes (I, II, or III), depending upon the amount of clinical information that existed to reasonably assure the FDA of the safety and

³⁷Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (May 28, 1976) (codified as amended in scattered sections of 21 U.S.C.).

³⁸21 U.S.C. §321(h) (2004), *amended by* Pub. L. No. 94-295, sec. 3(a)(1)(A), 90 Stat. 539.

³⁹*Id.* The 1976 Amendments, by eliminating this definitional overlap, served to overrule the 1969 decision in *United States v. An Article of Drug... Bacto-Unidisk...*, 394 U.S. 784, 793, 797 (1969). That decision defined “drug” within the FDCA to be much broader than the medical profession would define it, and then considered a “device” to have a parallel definition with only semantic differences.

effectiveness of the device.⁴⁰ Class I devices required neither a standard nor premarket approval because the general regulatory controls that the FDCA provided sufficiently guaranteed the device’s safety and effectiveness.⁴¹ A device that required more specialized controls (or “performance standards”⁴²) to exhibit safety and effectiveness under the FDCA was a Class II device, and those devices that required premarket approval⁴³ to provide reasonable assurance of their safety and effectiveness were Class III devices.⁴⁴ Class III also originally included all devices that were introduced for FDA approval following the 1976 Amendments (“postenactment devices”) that were not substantially equivalent to “preenactment devices.”⁴⁵

With the passage of the SMDA in 1990, Congress once again modified the definition of a “device.” Rather than barring a device from achieving “any of its principal” intended purposes through chemical action or being metabolized by the body, a device is now barred from achieving “its primary” intended purposes through those enumerated means.⁴⁶ The SMDA of 1990 also required the FDA to undertake a massive reclassification of currently regulated medical devices.⁴⁷ Section 515 of the FDCA was amended to require the FDA’s reconsideration of its classification of all preenactment Class III devices and mandated that those devices be reclassified as Class I or Class II, unless the FDA could show that the device properly belonged in Class III.⁴⁸

⁴⁰21 U.S.C. § 360c(a) (2004), *amended by* Pub. L. No. 94-295, sec. 2, 90 Stat. 539.

⁴¹*See* 21 U.S.C. § 360c(h); HUTT & MERRILL at 745.

⁴²*See* 21 U.S.C. § 360d.

⁴³*See* 21 U.S.C. § 360e.

⁴⁴21 U.S.C. § 360c(a)(1)(A)-(C).

⁴⁵*See* HUTT & MERRILL at 745.

⁴⁶*See infra* section II.A., note 102; 21 U.S.C. § 321(h)(3), *amended by* Safe Medical Devices Act of 1990 (hereinafter “SMDA”), Pub. L. No. 101-629, sec. 16(b)(2), 104 Stat. 4511 (November 28, 1990).

⁴⁷*See* HUTT & MERRILL at 750-51.

⁴⁸21 U.S.C. §§ 360c(e)-(f), 360e(i) (2004), *amended by* SMDA, Pub. L. No. 101-629, sec. 4(b), sec. 5, 104 Stat. 4511.

Currently, the regulation of medical devices in the United States rests with the Center for Devices and Radiological Health (CDRH) within the FDA.⁴⁹ Class I devices do not require premarket approval (PMA) nor do most Class I devices require any premarket notification (PMN).⁵⁰ Most Class II devices, however, do require a PMN, often known through its statutory shorthand as a “510(k)” because the PMN provisions are codified within section 510(k) of the FDCA.⁵¹ A 510(k) must be filed with and cleared by the CDRH prior to marketing of the device in the United States. The 510(k) must demonstrate that the device seeking FDA approval is either “substantially equivalent”⁵² to a device that has received premarket approval prior to the enactment of the 1976 Amendments, or to another device that the CDRH has already determined to be substantially equivalent.

A device that requires a PMA is a Class III device that poses a significant injury or illness risk, or a Class III device that was not substantially equivalent to a Class I or Class II device already approved under the 510(k) process.⁵³ Although a PMA is not as time-consuming or as expensive as an NDA for a new drug, the PMA is more difficult to obtain than a PMN and represents an actual approval by the CDRH.⁵⁴ Single-use Class III devices may also now be reprocessed and marketed in the United States, but the manufacturer must prepare first a premarket report (PMR) for submission to the FDA. The PMR is similar to a PMA, but it does not require the inclusion of information that explains how the device was originally manufactured or processed.⁵⁵ An unapproved medical device may be used in clinical trials on human subjects pursuant to

⁴⁹21 C.F.R. § 5.701(a)(2) (2004). See Center for Devices and Radiological Health, Device Advice, Overview of Regulations, at <http://www.fda.gov/cdrh/devadvice/overview.html> (last visited January 24, 2004).

⁵⁰A list of Class I and II devices that are exempt from a PMN can be found at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpd/315.cfm> (last visited January 24, 2004).

⁵¹21 U.S.C. § 360(k) (2004).

⁵²21 U.S.C. § 360c(i) (2004); 21 C.F.R. § 807(e) (2004); see *supra* note 48.

⁵³See *supra* n.48; see 21 U.S.C. §§ 360c(a)(1)(C(ii)(II)), 360e(a)-(b) (2004); 21 C.F.R. § 814 (2004).

⁵⁴*Id.*

⁵⁵21 U.S.C. § 379i(2) (2004), amended by MDUFMA, Pub. L. No. 107-250, sec. 102(a), 116 Stat. 1588 (October 26, 2002); see 21 U.S.C. §§ 360e(c)(1)-(2)(A) (2004), amended by MDUFMA, sec. 302(c)(2)(B).

an investigational device exemption (IDE). The proposed clinical trials must be first approved, however, by CDRH and an institutional review board (IRB).⁵⁶

For both a PMN and a PMA (and some PMA supplements), the device manufacturer must also submit a user fee in exchange for CDRH's review of the application.⁵⁷ Currently, the fee to file a PMA is roughly one hundred times greater than the fee that accompanies the filing of a PMN.⁵⁸ Between 1976 and 1991, more than 98 percent of new medical devices sought a PMN through substantial equivalence with a preenactment device.⁵⁹ The CDRH also performs varying levels of postmarket surveillance, ranging from mandatory surveillance of certain life-sustaining devices to discretionary surveillance of devices when it is necessary to protect the public health.⁶⁰

I. C. Biological Products

The federal Biologics Act, as originally passed in 1902, prohibited the interstate commercial sale or production of

“any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of disease or injuries of man...”⁶¹

⁵⁶ See *supra* n.48; 21 U.S.C. § 360j(g) (2004); 21 C.F.R. § 812 (2004).

⁵⁷ 21 U.S.C. § 379(j) (2004), amended by MDUFMA, Pub. L. No. 107-250, sec. 738, 116 Stat. 1588 (October 26, 2002).

⁵⁸ See Center for Devices and Radiological Health, Device Advice, PMA Review Fees, at <http://www.fda.gov/cdrh/devadvice/pma/userfees.html> (last visited April 16, 2004).

⁵⁹ See HUTT & MERRILL at 752.

⁶⁰ 21 U.S.C. §§ 360l(a)(1)-(2) (2004); see Center for Devices and Radiological Health, Postmarket Surveillance Studies, at <http://www.fda.gov/cdrh/devadvice/352.html> (last visited April 16, 2004).

This language was recodified within section 351 of the Public Health Services Act (PHSA) in 1944.⁶² In 1972, enforcement of the PHSA was delegated to the FDA⁶³ and in 1997, the FDA Modernization Act of 1997 (FDAMA) codified this language, with minor changes, to define a “biological product.”⁶⁴ One important distinction between biological products and drugs is that biological products are derived from living sources, whereas drugs are chemically synthesized.⁶⁵ At the same time, many biological products can also be classified as a “drug” under section 321(g)(1) of the FDCA and thus, the authority of the FDA to regulate biological products comes from two statutory sources.⁶⁶

As indicated above in section I.A., the approval and marketing of biological products (excepting therapeutic biologics, which have been transferred to the jurisdiction of CDER) in the United States is regulated by the Center for Biologics Evaluation and Research (CBER).⁶⁷ An investigational new drug application (IND) may be sought and obtained for a biological product as well as for a drug.⁶⁸ A new biological product, however, may be marketed within the United States only after CBER approves the manufacturer’s biologics license application (BLA). The approval of the BLA is conditioned upon demonstration of the safety, purity and potency of the new biological product.⁶⁹ This single BLA procedure replaced the old regime of licensing for biological products in 1999, when the requirement that the manufacturer obtain both an establishment license application (ELA) and a product license application (PLA) was eliminated.⁷⁰ Review of a BLA by CBER

⁶²42 U.S.C. § 262(a) (1944).

⁶³21 C.F.R. § 5.10 (2004); 37 Fed. Reg. 12865 (June 29, 1972).

⁶⁴42 U.S.C. § 262(i) (1997), *amended by* Food and Drug Administration Modernization Act of 1997 (hereinafter “FDAMA”), Pub. L. No. 105-115, sec. 123(d), 111 Stat. 2296 (November 21, 1997).

⁶⁵*See* Center for Biologics Evaluation and Research, at <http://www.fda.gov/cber/about.htm> (last visited April 16, 2004).

⁶⁶*Id.*

⁶⁷*See* 53 Fed. Reg. 8978 (March 18, 1988); 21 C.F.R. § 5.701(a)(1) (2004).

⁶⁸21 C.F.R. § 312.2(a) (2004).

⁶⁹21 C.F.R. § 601.2(d) (2004).

⁷⁰42 U.S.C. §§ 262(a)(2)(A)-(B) (2004), *amended by* Pub. L. No. 105-115, sec. 123(a)(1), 111 Stat. 2296; 64 Fed. Reg. 56441 (October 20, 1999).

is analogous to the review that CDER undertakes with each NDA. In fact, when Congress enacted FDAMA in 1997, it charged the FDA with the task of minimizing the differences in the review and the approval of NDAs and BLAs.⁷¹ Finally, postmarket reporting by the manufacturer of any adverse experiences with the biological product is required.⁷²

II. 1938-1990: The Changing Landscape of FDA-Regulated Products

As enacted, neither the original FDCA of 1938 nor the Medical Device Amendments of 1976 contemplated the regulation by the FDA of a product that was not solely a drug, a device, or a biological product, but was a combination of two or more of those categories. This result is perhaps not surprising in light of the prevalent technology when the original FDCA was enacted. The regulation of medical devices was added to the FDCA in 1938 not because of the technological advances in the field, but in large part to deter the marketing of fraudulent devices that increasingly occurred during the 1930s.⁷³ Further, the original FDCA did not provide for the regulation of biological products.⁷⁴ Moreover, the FDCA of 1938 expressly defined a “drug” and a “device” as exclusive of one another. It was not until the passage of the SMDA in 1990 that these two regulated categories were statutorily defined to be nonexclusive.⁷⁵ One decade after the enactment of the FDCA, however, technological innovation on the heels of World War II resulted in a near doubling of the number of domestic medical device manufacturers and a near quadrupling in the total value of

⁷¹Pub. L. No. 105-115, sec. 123(f), 111 Stat. 2296, 2324 (November 21, 1997).

⁷²21 C.F.R. § 600.80(c) (2004).

⁷³See HUTT & MERRILL at 720; S. REP. NO. 94-33, at 2-5 (1975). See also *supra*, n.11. Biologics are still defined under the Public Health Service Act, the administration of which was delegated to the FDA in 1972.

⁷⁴See *supra*, n.61.

⁷⁵See *supra*, n.17.

domestic industry shipments.⁷⁶ Especially during the 1960's, the medical device industry blossomed with the development of the pacemaker, kidney dialysis systems, and artificial cardiac valves and blood vessels.⁷⁷ Yet updated regulation over these increasingly sophisticated devices that often involved implantation in patients or accompanying medication regimens remained nonexistent, as the FDA had to furlough stricter regulation of medical devices in a legislative concession to ensure the passage of the 1962 Drug Amendments.⁷⁸

Once the 1976 Medical Device Amendments were passed, there was still no mention of, or provision for, a scheme of regulation to control the approval of products that fit into more than one regulated category. Perhaps this is so for two reasons. The FDA had only recently been delegated the responsibility of regulating biological products.⁷⁹ Second, the 1976 Amendments were narrowly focused upon modernizing the FDCA by broadening its regulatory reach sufficiently to respond to the medical devices that resulted from the technological boom.⁸⁰ Hence there was the creation of the device classes and the corresponding approval procedures for each class. Despite the continued lack of explicit statutory guidance, the FDA forged ahead. Through numerous case-by-case decisions in the 1970s and 1980s, the FDA assigned or adjusted to the three main Centers approval jurisdiction over those products occupying the border between drugs, devices, and biological products. A few examples illustrate the diversity of the situations that the FDA encountered.

In the early 1970's, the first sign of combination products appeared on the FDA's regulatory landscape.

Products such as radiobiologicals, radiopharmaceuticals, and *in vitro* diagnostic products explicitly required

⁷⁶See Theodore H. Cooper, *Device Legislation*, 26 FDC L. J. 165 (1971)(from 1937 to 1947, the number of American medical device manufacturers increased from 463 to 980 and the total value of medical device shipments within the United States increased from a little over one million dollars to \$3.72 million annually).

⁷⁷S. REP. NO. 94-33, at 5 (1975).

⁷⁸See HUTT & MERRILL at 743.

⁷⁹See *supra*, n.63.

⁸⁰See Cooper, *supra*, n.76 (nearly 1500 medical device manufacturers, with total annual shipments in excess of \$1.5 billion, in 1967).

the FDA to determine in which Center each of those products would be regulated.⁸¹ Pursuant to the passage of the 1976 Medical Device Amendments, certain “transitional” devices that the FDA had traditionally regulated as drugs were redesignated automatically as Class III devices, requiring an approved PMA to enter the market.⁸² In 1979, the Bureau of Biologics (a predecessor of CBER) was assigned the lead jurisdiction for the regulation of medical devices that processed or administered biological products.⁸³ The predecessor of CDRH, the Bureau of Medical Devices, initially received lead jurisdiction to regulate *in vitro* biological diagnostic products in 1980.⁸⁴ The FDA decided that it could not regulate attached cigarette filters as medical devices in 1982.⁸⁵ In 1986, analytical products that were used to test for a certain chemical allergy in humans were designated as biological products.⁸⁶ By 1989, the FDA’s regulatory practices had established a trend that treated combination products that consisted of a medical device and a drug as a device only, as long as the drug was employed according to the use that was approved by the FDA.⁸⁷ In 1990, *in vitro* diagnostic products that detected antibodies to hepatitis B core antigens were switched from regulation as medical devices to regulation as biological products because they began to be used primarily to screen blood transfusions.⁸⁸ In contrast, an *in vitro* radioimmunoassay test that detected the abuse of certain drugs through human hair analysis was designated as a medical device, requiring a PMA.⁸⁹ To this day, any application that is made by a drug manufacturer to the FDA for a new drug that also contains biological components must be addressed to CBER, rather than CDER.⁹⁰

⁸¹56 Fed. Reg. 58754-01, 1991 WL 242348 (November 21, 1991).

⁸²See 21 U.S.C. § 360j(1) (2004), *amended by* Pub. L. No. 94-295, sec. 520, 90 Stat. 539 (May 28, 1976); 42 Fed. Reg. 63472 (December 16, 1977) (listing transitional devices).

⁸³See 44 Fed. Reg. 24236 (April 24, 1979), 47 Fed. Reg. 15412-01 (April 9, 1982).

⁸⁴See 45 Fed. Reg. 51226 (August 1, 1980), 45 Fed. Reg. 58964-02 (September 5, 1980), 47 Fed. Reg. 34532-01 (August 10, 1982), 51 Fed. Reg. 37976-03 (October 27, 1986). *But see infra* Section III.D.3.

⁸⁵See 47 Fed. Reg. 31130, 31132 (July 16, 1982).

⁸⁶See 51 Fed. Reg. 33664-01 (September 22, 1986).

⁸⁷See *e.g.*, 21 C.F.R. § 876.5820 (2004)(regulation of hemodialysis system and accessories).

⁸⁸See 55 Fed. Reg. 5892-02 (February 20, 1990).

⁸⁹See 55 Fed. Reg. 23985-01 (June 13, 1990).

⁹⁰See 21 C.F.R. § 312.140; 21 C.F.R. § 312.440 (2004).

Faced with a product market that was increasingly diverse and sophisticated, as well as an ad hoc regime of assigning responsibility for those products, each of the three Centers entered into Intercenter Agreements with each of the other Centers, beginning in 1982. The agreements were designed to minimize repetitive and conflicting regulation, to inform manufacturers, and to conserve agency resources.⁹¹ All three of these agreements first determined which Center would have approval jurisdiction for a given type of product and then provided guidance to the product manufacturer as to the working relationship between each Center during the approval process.

Coordination between the Bureau of Biologics (BoB), the Bureau of Medical Devices (BMD), and the Bureau of Radiological Health (BRH) was the first cooperative agreement to exist when the three bureaus signed an agreement in 1982 to identify separate responsibilities in the oversight of medical devices.⁹² The agreement was still in effect, even after BMD and BRH first united in March, 1982 to form CDRH and BoB eventually became CBER.⁹³ The agreement that arose between CDER and CBER did not predate this CBER-CDRH agreement because CDER and CBER did not separate from one another again until 1988.⁹⁴ Their agreement, however, represented simply a continuation of an existing working relationship to regulate the frontier between drugs and biological products.⁹⁵ Finally, the agreement between CDER and CDRH was the formal culmination of multiple, previous ad hoc collaborations (a few examples of which were illustrated

⁹¹U.S. Food and Drug Administration, Office of Combination Products, Intercenter Agreements, at <http://www.fda.gov/oc/combination/intercenter.html> (last visited April 16, 2004).

⁹²See 47 Fed. Reg. 15412-01 (April 9, 1982).

⁹³*Id.*; U.S. Food and Drug Administration, Office of Combination Products, Intercenter Agreements, Biologics & Devices Intercenter Agreement, at <http://www.fda.gov/oc/ombudsman/bio-dev.htm> (last visited April 16, 2004) (hereinafter “CBER-CDRH Intercenter Agreement”).

⁹⁴See *supra*, n.22.

⁹⁵U.S. Food and Drug Administration, Office of Combination Products, Intercenter Agreements, Intercenter Agreement between CDER and CBER, at <http://www.fda.gov/oc/ombudsman/drug-bio.htm> (last visited April 16, 2004) (hereinafter “CDER-CBER Intercenter Agreement”).

above).⁹⁶ It became effective in late October, 1991, as did the latest version of the other two agreements, because changes were necessary to reflect the mandatory provisions of the SMDA.⁹⁷ The working relationship between each Center will be explored in more detail *infra*.

By 1990, the number of sophisticated new products that sought FDA approval and that also potentially implicated the expertise of more than one Center continued to increase. An extensive Congressional hearing before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce occurred early in 1990 to address the failure of the Bjork-Shiley Convexo-Concave heart valves, previously approved by CDRH and the FDA.⁹⁸ During that hearing, a report was introduced by CDRH highlighting some of the devices that had recently received approval. This report served as an indication of the level of complexity that CDRH experienced in regulating devices that interacted with the human body. A few of the examples included anesthesia machines that delivered certain anesthetic gases and oxygen to humans in patient-specific dosages,⁹⁹ hemodialysis machines that intravenously filtered wastes from the blood of a patient (who was often totally dependent upon that machine for survival)¹⁰⁰ and home use *in vitro* diagnostic (IVD) devices that screened for medical conditions such as pregnancy, blood glucose, urinary tract infections, and gonorrhea.¹⁰¹ The CDRH report at the Shiley heart valve hearing made clear that the FDA needed a more sophisticated statutory grant to acknowledge the changing horizon of its approval landscape.

⁹⁶U.S. Food and Drug Administration, Office of Combination Products, Intercenter Agreements, Intercenter Agreement between CDER and CDRH, at <http://www.fda.gov/oc/ombudsman/drug-dev.htm> (last visited April 16, 2004) (hereinafter “CDER-CDRH Intercenter Agreement”).

⁹⁷56 Fed. Reg. 58760-01 (November 21, 1991).

⁹⁸*FDA and the Medical Device Industry: Hearing Before the Subcomm. on Oversight and Investigations of the House Comm. on Energy and Commerce*, 101st Cong. 203 (1990).

⁹⁹*Id.* at 242-43.

¹⁰⁰*Id.* at 259-60.

¹⁰¹*Id.* at 261-62.

III. The Safe Medical Devices Act (SMDA) of 1990: Its Origins and Its Impact

III.A. Section 16 of the SMDA

The Shiley heart valve hearing took place just nine months before the passage of the SMDA of 1990. In the intervening months, both Houses of Congress worked independently on bills meant to modernize the regulation of medical devices by amending the provisions of the FDCA. The result was the SMDA. Within the SMDA, a provision appeared that finally and formally recognized the presence of the combination product on the FDA's regulatory radar. Congress for the first time codified how FDA was to exercise its jurisdiction over a product that was not solely a drug, a medical device, or a biological product within section 353(f) of the FDCA. The Secretary of Health and Human Services was delegated the power to “designate a component of the Food and Drug Administration to regulate products that constitute a *combination of a drug, device, or biological product.*”¹⁰² (emphasis added). Some explanation of the drafting of this pertinent provision and its inclusion within the SMDA may illustrate how slowly both our administrative and legislative mechanism responded to the onslaught of combination products.

During August 1990, Senator Edward Kennedy, as the Chair of the Labor and Human Resources Committee, joined by four other Senators introduced a Senate bill entitled the “Comprehensive Medical Device Improvement Act” (S. 3006).¹⁰³ As the title of the bill made clear, one purpose of this legislation was to build upon

¹⁰²21 U.S.C. § 353(g)(1) (2004); 21 C.F.R. § 3.2(e) (2004).

¹⁰³Comprehensive Medical Device Improvement Act, S. Res. 3006, 101st Cong. (1990). See 135 Cong. Rec. S12476-02, S12487 (August 4, 1990).

the improvements to the FDCA made through the Medical Device Amendments of 1976 by allowing the medical device industry to “benefit from more consistent FDA regulation” while “encourag[ing] technological innovation” and “providing improved protections for public health.”¹⁰⁴ One further purpose of S. 3006, as pointed out by Senator Kennedy, was to “improve efficiency in the FDA review process by providing that the Secretary will require only one market clearance route for products which are combinations of devices, drugs, or biologics.”¹⁰⁵ Senator Dodd echoed Senator Kennedy’s sentiments and added that the “tremendous diversity in the medical devices industry” made this bill necessary. More particularly, he noted that this diversity had stood in the way of the FDA’s effective implementation of the Medical Device Amendments of 1976 because of the complexities of those Amendments, the FDA’s interpretation of the Amendments, and the FDA’s limited resources.¹⁰⁶ One other sponsor, Senator Durenberger from Minnesota, supported the new provisions related to combination product regulation because his constituency was comprised in part of medical device companies.¹⁰⁷ To that end, section 20 of S. 3006 was drafted to amend section 503 of the FDCA with the following language:

SEC. 20. REVIEW OF MARKET APPLICATIONS FOR ARTICLES
COMPRISING COMBINATIONS OF DRUGS, DEVICES OR BIOLOG-
ICS

Section 503 (21 U.S.C. 353) is amended-

(1) by striking the section heading and inserting the following:

*SPECIAL CONSIDERATION FOR CERTAIN DRUGS, DEVICES,
AND BIOLOGICAL PRODUCTS;*

¹⁰⁴ *Id.* at S12487-89.

¹⁰⁵ *Id.* at S12489.

¹⁰⁶ *Id.*

¹⁰⁷ *Id.* at S12495.

and

(2) by adding at the end the following new subsection:

(f)(1) *The Secretary shall require only one market clearance route for an article that constitutes a combination of a device, drug, or biological product. If the Secretary determines that the primary mode of action of the combination article is that of-*

(A) a drug (other than a biological product), neither the combination article nor any part of the article shall be treated as a device or as a biological product for market clearance purposes;

(B) a device, neither the combination article nor any part of the article shall be treated as a drug or a biological product for market clearance purposes; or

(C) a biological product, neither the combination article nor any part of the article shall be treated as a drug or a device for market clearance purposes.

(2) Nothing in this paragraph shall prevent the Secretary from using any agency resource of the Food and Drug Administration necessary to assure adequate review of the safety, effectiveness, or substantial equivalence of an article, if the Secretary employs a single market clearance mechanism.

(3) The Secretary shall promulgate regulations to implement market approval procedures in accordance with paragraph (1) not later than 1 year after the date of enactment of this subsection.

(4) As used in this subsection:

(A) The term 'biological product' has the meaning given the term in section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)).

(B) The term 'market clearance' includes approval of an application under section 505, 507, 515, or 520(g), an order determining substantial equivalence under this subchapter, and approval of a product or establishment license under subsection (a) or (d) of section 351 of the Public Health Service Act (42 U.S.C. 262).¹⁰⁸ (emphasis added).

Just over two months later, on October 5, 1990, the Committee on Energy and Commerce within the House of Representatives presented its report on a House bill (H.R. 3095), otherwise known as the Safe Medical Devices Act of 1990.¹⁰⁹ This report was presented to the House just one month before the passage of the SMDA by Congress, containing the major provisions that would eventually be codified within the FDCA. Yet no provision within H.R. 3095 mentioned combination products in any way.

¹⁰⁹H.R. 3095, 101st Cong. (1990) (enacted). See H. REP. NO. 101-808, 1990 WL 200530 (October 5, 1990).

Four days later, the Senate was presented with a report from the Committee on Labor and Human Resources recommending passage of an amended version of S. 3006.¹¹⁰ The pertinent language from the amended section 20 of S. 3006 is reprinted below, so as to be contrasted with the earlier version reproduced in italics *supra*.

SEC. 20. REVIEW OF MARKET APPLICATIONS FOR ARTICLES
COMPRISING COMBINATIONS OF DRUGS, DEVICES, AND BIO-
LOGICS.

Section 503 (21 U.S.C. 353) is amended-

(1) by striking the section heading and inserting the following:

*EXEMPTIONS AND CONSIDERATION FOR CERTAIN DRUGS,
DEVICES, AND BIOLOGICAL PRODUCTS;*

¹¹⁰S. REP. NO. 101-513, 1990 WL 201762 (October 9, 1990).

and

(2) by adding at the end the following new subsection:

(f)(1) The Secretary shall designate a component of the Food and Drug Administration to regulate products that constitute a combination of a drug, device, or biological product. The Secretary shall determine the primary mode of action of the combination product. If the Secretary determines that the primary mode of action is that of-

(A) a drug (other than a biological product), the persons charged with premarket review of drugs shall have primary jurisdiction;

(B) a device, the persons charged with premarket review of devices shall have primary jurisdiction; or

(C) a biological product, the persons charged with premarket review of biological products shall have primary jurisdiction.

(2) Nothing in this subsection shall prevent the Secretary from using any agency resources of the Food and Drug Administration necessary to ensure adequate review of the safety, effectiveness, or substantial equivalence of an article. (3) The Secretary shall promulgate regulations to implement market approval procedures in accordance with paragraphs (1) and (2) not later than 1 year after the date of enactment of this subsection.

(4) As used in this subsection:

(A) The term 'biological product' has the meaning given the term in section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)).

(B) The term 'market clearance' includes-

(i) approval of an application under section 505, 507, 515, or 520(g);

(ii) a finding of substantial equivalence under this subchapter; and

(iii) approval of a product or establishment license under subsection (a) or

(d) of section 351 of the Public Health Service Act (42 U.S.C. 262).¹¹¹

This amendment to S. 3006 contains the final version of the provision that explicitly governs the FDA's pre-existing regulatory control over combination products, as it also appeared within section 16 of the SMDA and as it was codified within section 503 of the FDCA.¹¹² The most obvious and noteworthy difference between the two versions was the removal of the earlier language "requir[ing] one market clearance route" in favor of a more broad designation directing the FDA to "regulate products that constitute a combination." In addition, the earlier version required that once the FDA determined the primary mode of action of the product, that primary mode would guide the product's approval process to such an extent that "neither the combination

¹¹²SMDA, Pub. L. No. 101-629, sec. 16(a), 21 U.S.C. § 353(f) (1990).

article nor any part of the article” would be treated as anything other than pertaining to that primary mode for market clearance purposes.¹¹³ As the later version of section 20 makes clear, the Senate eased those restrictions by granting “primary jurisdiction” to the Center that normally oversees products with that primary mode of action.¹¹⁴ That Center would be responsible for reviewing the premarket submission of the entire combination product.¹¹⁵ Such language allows for the cooperative input of the other Centers during the approval process.

The report that accompanied the amended version of S. 3006 echoed Senator Kennedy’s statements two months earlier with regard to lessening product over-regulation by the FDA while maintaining an innovative medical device industry. Yet the report went further than the previous comments on the Senate floor as it explained the intent behind adding section 20 to regulate combination products. The Labor and Human Resources Committee recognized the “difficulty under the present law in determining the jurisdictional base for regulating products that are comprised of combinations of drugs, devices, or biologics,” and made note of the industry view that the FDA’s premarket review process was weak in determining how to regulate combination products.¹¹⁶ The delays that combination product manufacturers felt due to this regulatory weakness spurred the Senate to “provide the Secretary with firm ground rules to direct products promptly to that part of the FDA responsible for reviewing the article that provides the primary mode of action,” especially since the number of combination products coming before the FDA for approval was increasing.¹¹⁷

Section 20 was drafted to “eliminate the need to receive clearances from both the device and drug review

¹¹³See *supra* n.108.

¹¹⁴See *supra* n.111.

¹¹⁵S. REP. NO. 101-513, VI. Section-By-Section Analysis, Section 20, 1990 WL 201762 (October 9, 1990).

¹¹⁶*Id.* at IV. Committee Views, Sections 19 and 20.

¹¹⁷*Id.*

divisions, and will vest authority in one agency group to conduct a premarket review.”¹¹⁸ The Committee was quick to caution, however, that the goal of administrative efficiency within the FDA would not exempt the manufacturer from producing the same level of safety and effectiveness data for each component of the combination product.¹¹⁹

Just over two weeks later, Representative Waxman submitted a conference report to the House of Representatives.¹²⁰ The report was the result of a conference that was necessary to resolve the differences between H.R. 3095 and S. 3006. The Senate, when presented with H.R. 3095, had replaced all of the provisions with the text of S. 3006; the House had responded by amending S. 3006 and replacing some of the language of H.R. 3095 again.¹²¹ The conference version of H.R. 3095 that resulted was an amalgamation of the two bills, and it was the final bill that would be passed by both Houses,¹²² presented to the President, and enacted at the close of 1990 as the SMDA. With respect to combination products, this conference report is of note because the conference managers from both Houses agreed to the inclusion of section 20 of S. 3006 within the final bill.¹²³

In the aftermath of the passage of the SMDA, the definition of a medical device itself had to be altered because section 16 of the SMDA, formerly section 20 of S. 3006, provided for combination product regulation by a

¹¹⁸*Id.*

¹¹⁹*Id.*

¹²⁰H.R. CONF. REP. NO. 101-959 (1990). *See* 136 Cong. Rec. H13251-01, 1990 WL 290412 (October 26, 1990).

¹²¹*Id.* at H13256.

¹²²*See* 136 Cong. Rec. H13008-01 (October 26, 1990) (House acceptance of the conference report); *see* 136 Cong. Rec. S17456-01, S17458 (October 27, 1990) (Senate acceptance of the conference report). Sen. Durenberger in particular expressed his gratitude toward the “inclu[sion] of the Senate provision on products which are comprised of combinations of devices, drugs, or biologics. These so-called combination products are, and will continue to be, of great benefit to health care consumers, and I think it is important that we acted to streamline the regulatory barriers facing such products.”

¹²³136 Cong. Rec. at H13259.

specific Center based upon the product's "primary mode of action."¹²⁴ The primary mode of action of the product was determined once the product's effect upon the body and the relative contribution of each of its components was assessed.¹²⁵ If the primary mode of action was not determinable in that manner, then other factors such as guidance from the Intercenter Agreements or a determination of the most innovative component of the product that posed the greatest safety risk or clearest indication of use would guide the FDA in deciding to which Center jurisdiction would be granted.¹²⁶ Once approval and oversight jurisdiction of each product was thus awarded, Congress needed to redefine a "device" in terms of "its primary" purpose rather than "any of its principal purposes" to comply. In 1991, Congress amended the FDCA to move section 16 of the SMDA and its "primary mode of action" language to its current resting place within section 353(g).¹²⁷

III.B. The Effect of the SMDA on the FDA's Regulatory Framework

With the statutory mandate of the SMDA to oversee and approve combination products added to the FDA's responsibilities, the FDA next undertook administrative proceedings to adapt its regulatory framework by November 29, 1991, the one-year deadline set by the SMDA.¹²⁸ Such an adaptation would give each Center and each product manufacturer guidelines to adhere to throughout the approval process. On November 21, 1991, the FDA announced final regulations containing the new provisions in 21 C.F.R. §§ 3.1-10 (1991) "to describe how the agency will determine which component within FDA will have primary jurisdiction for the

¹²⁴Pub. L. No. 101-629, sec. 16(a)(2), 104 Stat. 4511; 56 Fed. Reg. 58754 (November 21, 1991); 21 C.F.R. § 3.1 (2004).

¹²⁵21 C.F.R. § 3.4(a) (2004); 56 Fed. Reg. 58754 (November 21, 1991); 67 Fed. Reg. 34722 (May 15, 2002).

¹²⁶21 C.F.R. § 3.5; *see* 21 C.F.R. §§ 3.7(a)-(b) (2004).

¹²⁷Nutrition Labeling and Education Act of 1990, Amendment, Pub. L. No. 102-108, sec. 2(d)(4), § 353(g), 105 Stat. 549, 550 (August 17, 1991).

¹²⁸56 Fed. Reg. 58754-01, 1991 WL 242348 (November 21, 1991).

premarket review and regulation of: (1) A combination drug, device, or biologic product or (2) any drug, device, or biologic product where the center with primary jurisdiction is unclear or in dispute. This rule describes how to identify the agency's assigned review component which will, in most cases, eliminate the need for a sponsor to obtain approval from more than one FDA component for a combination product."¹²⁹ In light of this change in its approval procedures, the FDA decided that its approval efficiency would be enhanced by also applying these new rules in the future to any product whose approval jurisdiction was disputed or unclear. The rules would not be limited to only those combination products as defined by the SMDA.¹³⁰ The FDA explicitly excluded from that regulation, however, most drugs, devices or biological products that are used concomitantly as well as products that are comprised exclusively of two or more drugs, two or more devices, or two or more biological products.¹³¹

Since these new regulations would bind both the Centers within the FDA and the combination product manufacturers, the FDA stepped beyond the basic definition of a combination product as provided by the SMDA, and used the new regulations to provide a few illustrative examples of how the SMDA definition could be interpreted.¹³² The term "combination product" now encompassed

(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

¹²⁹ *Id.*

¹³⁰ 21 C.F.R. §§ 3.1, 3.3 (1991). 56 Fed. Reg. at 58756. *See also* 21 U.S.C. § 353(g)(1) (2004).

¹³¹ *Id.* at 58755.

¹³² *Id.* at 58754-55.

(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.¹³³

Paragraph (1) comports as expected with the literal definition of a combination product as given by the SMDA. Paragraphs (2) – (4), by contrast, represent the influence of other industry considerations uniquely within the purview of FDA’s regulatory knowledge.

One explanation for the inclusion of paragraphs (2) – (4), regulating both products that are packaged together and products that are packaged separately but labeled in such a manner so as to be used together, is the influence of the other administrative responsibilities of the FDA. The SMDA was enacted in part to ensure the safety and effectiveness of medical devices by modernizing the standards of premarket review applied to those devices.¹³⁴ As these regulations stated, though, “nothing in this section [16 of the SMDA] prevents FDA from using any agency resources it deems necessary to ensure adequate review of the safety and effectiveness of any product.”¹³⁵ As mentioned *supra*, the FDA also monitors the labeling and packaging of drugs, medical devices, and biological products as part of its administrative role.¹³⁶ Thus, Congress may have considered a product to represent a combination only if the parts of the combination were in physical

¹³⁴ See *supra* n.102.

¹³⁵ 21 C.F.R. § 3.1 (1991).

¹³⁶ See *supra* n.13.

proximity to one another, given the original language of section 20 of S. 3006 and the final codified language of section 16 of the SMDA.

But the FDA, through this rule, expressed an understanding that classification as a combination product may extend beyond the immediate appearance of the product (or its parts) to the manner in which the product is *employed* by the end consumer. Two items that are packaged separately, but are intended to be used in conjunction with one another for the benefit of the patient, will be treated as a combination product by the health professional administering the product. The separate parts, then, are best regulated as a combination product by the FDA as well to ensure the overall safety of the product and the patient, in accordance with the statutory charge of the SMDA.

After explaining the purpose of these new regulations in response to the SMDA, providing definitions to industry terms appearing within the regulations, and clarifying their scope, the FDA reiterated that the product's "primary mode of action" would be the primary determinant in assigning Center premarket review jurisdiction.¹³⁷ The FDA did make one important addition, however, to the provisions of the SMDA regarding the primary mode of action. The original language of section 20 of S. 3006 granted approval jurisdiction to only one Center for "market clearance purposes."¹³⁸ Yet that language was softened, perhaps in response to the disagreement by the House in H.R. 3095 and as a concession by the Conference Committee, such that section 16 of the SMDA gave to the Center responsible for reviewing the product's primary mode of action only "primary jurisdiction." To cement this new statutory position within the FDCA, the FDA

¹³⁷21 C.F.R. § 3.4 (1991). 56 Fed. Reg. at 58756-57. *See also* 21 U.S.C. § 353(g)(1) (2004).

¹³⁸*See supra* III.A., n.108.

provided that “the designation of one agency component as having primary jurisdiction for the premarket review and regulation of a combination product *does not preclude consultations by that component with other agency components or, in appropriate cases, the requirement by FDA of separate applications*”¹³⁹ (emphasis added).

In a corresponding fashion, the three Intercenter Agreements,¹⁴⁰ discussed *infra* in II.C., were updated at approximately the same time that these regulations were promulgated to reflect the changes effected by the SMDA in favor of greater intercenter cooperation. The FDA drew attention to the existence of these non-binding documents to inform combination product manufacturers and the public by citing them in the new regulations.¹⁴¹ Section 3.5(a)(3) of these regulations encouraged the manufacturer to contact the appropriate Center before beginning the premarket review process to discuss the Center’s jurisdiction and to settle any questions. This provision evinces the policy that initially motivated the SMDA: greater communication between the industry manufacturer and the FDA to enhance the efficiency of the regulatory process and to increase the public safety.

The remaining regulations, published in November 1991, elucidated the actual steps to be taken by a product manufacturer prior to a premarket review.¹⁴² Section 3.7 detailed the “who, when, what and where” for the product manufacturer wishing to file a letter of request for designation.¹⁴³ Section 3.8 explained that a

¹³⁹21 C.F.R. § 3.4(b) (1991). 56 Fed. Reg. at 58756-57.

¹⁴⁰*See also supra* n. 91.

¹⁴¹21 C.F.R. § 3.5 (1991); 56 Fed. Reg. at 58757.

¹⁴²21 C.F.R. §§ 3.7-.10 (1991); 56 Fed. Reg. at 58757-58.

¹⁴³21 C.F.R. § 3.7 (1991). A “letter of request means an applicant’s written submission to the product jurisdiction officer seeking the designation of the agency component with primary jurisdiction.” 21 C.F.R. § 3.2(j) (1991); 56 Fed. Reg. at 58756.

letter of designation would be sent back to the manufacturer within sixty days of the request “specifying the agency component designated to have primary jurisdiction for the premarket review and regulation of the product at issue, and any consulting agency components.”¹⁴⁴ The product manufacturer, if unhappy with the agency’s decision, could request a reconsideration within fifteen days of receiving the letter of designation; the agency would then be given fifteen additional days to review the designation and respond.¹⁴⁵ Finally, a letter of designation would represent a final FDA determination unless the product jurisdiction officer (in this case, the FDA Ombudsman¹⁴⁶) changed the designation with the manufacturer’s consent or without the manufacturer’s consent because of concerns about the public health “or other compelling reasons.”¹⁴⁷ The manufacturer would be entitled to object to such a nonconsensual change and the FDA would be required to respond in writing with reasons for the change.¹⁴⁸

III. C. 1991: The New Intercenter Agreements

In response to the statutory and regulatory changes that the SMDA effected within the FDA as a whole, each Center within the FDA needed to modernize its individual approach toward combination products. The Intercenter Agreements that resulted late in 1991 thus determined the role of each Center when the expertise of two or more Centers was involved in the approval of a combination product. Predictably, each of their traditional roles was maintained. CDRH still maintained lead jurisdiction for approving medical

¹⁴⁴21 C.F.R. § 3.8(b) (1991). A “letter of designation means the written notice issued by the product jurisdiction officer specifying the agency component with primary jurisdiction for a combination product.” 21 C.F.R. § 3.2(i) (1991); 56 Fed. Reg. at 58756.

¹⁴⁵21 C.F.R. § 3.8(c) (1991).

¹⁴⁶21 C.F.R. § 3.6 (1991); 56 Fed. Reg. at 58757.

¹⁴⁷21 C.F.R. § 3.9 (1991); 56 Fed. Reg. at 58757.

¹⁴⁸21 C.F.R. § 3.9(b) (1991). As an extra administrative check on a nonconsensual change in designation, the product jurisdiction officer’s decision “requires the concurrence of the Deputy Commissioner for Operations or the Deputy Commissioner for Policy.” *Id.*

devices, CDER still oversaw the approval of new drugs, and CBER still regulated the presence of biological products in the American market. The modernization efforts that were set into motion by the SMDA, however, could not be fully realized without the cooperation of each of the other Centers. As a result, the Intercenter Agreements specified that premarket review of combination products would require the Centers either to divide their jurisdiction pursuant to the guidelines established by the pertinent Agreement or work cooperatively to oversee the tailored approval process.

Each Agreement also provided for an Intercenter Jurisdictional Committee, an ad hoc group comprised of one regular member and one alternate from each Center. The committee would resolve questions that arose over the manner in which jurisdiction for product approval had been assigned. Any disagreement within the committee would result in an application of the product jurisdiction procedures. These procedures, sometimes called the “request for designation” (RFD) process,¹⁴⁹ also would be available at the initial request of the product manufacturer for a formal agency determination of which Center would have approval jurisdiction.¹⁵⁰

III. C. 1. CBER-CDRH Intercenter Agreement

Combination products that were subject to the CBER-CDRH Agreement included those products that represented advances in medical device technology for biological applications or biological products coupled

¹⁴⁹See *supra* III.B., n.143.

¹⁵⁰See U.S. Food and Drug Administration, Office of Combination Products, Jurisdictional Updates, at <http://www.fda.gov/oc/combination/updates.html> (last visited April 16, 2004).

with medical devices for therapeutic use.¹⁵¹ CDRH was designated the lead Center to manage any good manufacturing practices (GMP) problems in addition to all of the medical device reporting issues that arose as a result of the premarket review process.¹⁵² In contrast, both CBER and CDRH would *share* jurisdiction over other aspects of the approval process, including surveillance and FDCA compliance, informal and formal sanctions, PMNs, IDEs, PMAs and petitions for device reclassification and exemptions.¹⁵³

Formal approval responsibility for medical devices, however, was *divided* between the Centers in the following ways. CDRH would retain general approval responsibility, but CBER became generally responsible for regulating “medical devices used or indicated for the collection, processing, storage or administration of blood products, blood components or analogous products, as well as screening or confirmatory clinical laboratory tests associated with blood banking practices and other process testing procedures” as well as any *in vitro* test kits and any medical devices intended for use for HIV and other retroviruses.¹⁵⁴ The Agreement provided a few examples of these devices, including collection devices, specimen containers, components of test kits and those devices used for the inactivation of HIV and other retroviruses.¹⁵⁵ CBER was also assigned the approval jurisdiction to regulate some generic medical devices that the CDRH originally classified in its hematology category.¹⁵⁶ CDRH would regain responsibility, though, if the device had a therapeutic purpose, meaning that the device was intended for a specific use on a particular patient with a specific ailment to provide a direct clinical benefit for that patient.¹⁵⁷

¹⁵¹ See CBER-CDRH Intercenter Agreement, *supra* n.93.

¹⁵² *Id.* at section III.

¹⁵³ *Id.* at section IV.

¹⁵⁴ *Id.* at section VI.

¹⁵⁵ *Id.*

¹⁵⁶ *Id.* at section VII.

¹⁵⁷ *Id.* at section VI.

III.C. 2. CDER-CDRH Intercenter Agreement

These two Centers were accustomed to cooperating prior to their 1991 Agreement,¹⁵⁸ but both recognized that the statutory amendments created the SMDA would require a codification of their working relationship rather than a continuation of their history of ad hoc decision-making.¹⁵⁹ To some extent, this Agreement mirrored the CBER-CDRH agreement, in that CDRH and CDER shared the same subelements of jurisdiction over the general aspects of the approval process as do CBER and CDRH.¹⁶⁰ Similarly, the two Centers in this Agreement strove to assure manufacturers that approval for their product usually would be necessary from only one Center.¹⁶¹ To that end, the Agreement provided in some detail the criteria that CDER and CDRH would consider in designating a product as a drug, device, or a combination thereof before assigning approval jurisdiction.¹⁶²

In addition, the Agreement explained how the two Centers would manage the approval of a few important, common product designs. The category that the product would be placed in (drug, device, or combination product), the steps of approval (including the appropriate application mechanism) and the subsequent role of each Center was outlined. First, the Agreement indicated in what special circumstances the approval of both Centers still would be required, such as when the product was a device that primarily delivered or helped to deliver a drug, but that drug is not distributed with the device.¹⁶³ Another example was a device that

¹⁵⁸ See *supra* n.93.

¹⁵⁹ See CDER-CDRH Intercenter Agreement, *supra* n.96.

¹⁶⁰ See *id.* at section IV.

¹⁶¹ See *id.* at section V. See also *id.* at section VI; CBER-CDRH Intercenter Agreement, *supra* n.93 at section V. (allowing for the possibility of a collaborative review between the two Centers, even though the regulations contained within 21 C.F.R. Part 3 encourage the grant of approval jurisdiction to just one Center).

¹⁶² *Id.* at section VIII.

¹⁶³ *Id.* at section VII.A.1(a).

was used concurrently with a drug to activate or improve the benefit of the drug.¹⁶⁴ Second, the Agreement maintained a default category in which ad hoc jurisdictional decisions still would be appropriate.¹⁶⁵ Products traditionally considered to be drugs and devices, respectively, would retain that designation, except those drugs that were affected by the Transitional Device Notice in 1977.¹⁶⁶

Finally, the Agreement indicated what types of new products could anticipate being categorized as combination products and what Center would have subsequent primary jurisdiction over their approval. Medical devices that were pre-filled with drugs to deliver, or devices that incorporated the drug in general within the overall product as part of the functioning of the device, were both examples of combination products, except that CDER would oversee the former and CDRH would oversee the latter.¹⁶⁷ Further examples included a drug that incorporated a device component to effect the function of the drug (overseen by CDER),¹⁶⁸ a drug and a device combined together that would process the drug into its final packaged form (CDER),¹⁶⁹ and a device kit that was both labeled for use with a certain drug and was packaged with that drug as a means of effectuating the function of the device (CDRH).¹⁷⁰ An interesting exception to these standards was a device that would be used to produce a drug that was delivered directly to the patient or was used at a medical facility. The product would be classified a device, yet regulated by CDER.¹⁷¹

III. C. 3. CDER-CBER Intercenter Agreement:

¹⁶⁴*Id.* at section VII.B.1.

¹⁶⁵*Id.* at section VII.E.

¹⁶⁶*Id.* at section VII.C.-D. *See also supra*, n.82.

¹⁶⁷*See id.* at section VII.A.1(b)-A.2.

¹⁶⁸*See id.* at section VII.A.3.

¹⁶⁹*See id.* at section VII.A.4(b).

¹⁷⁰*See id.* at section VII.B.2.

¹⁷¹*See id.* at section VII.A.4(a).

Taking yet another approach than the CDER-CDRH Agreement, CDER and CBER chose to designate approval jurisdiction for a drug or biological product depending upon the product class.¹⁷² A product class was defined to be a “distinct category of agents recognizable by physical characteristics, source materials or pharmacologic properties.”¹⁷³ The Agreement provided a few examples of these classes: vaccines, hormones, and antibiotics. When one Center was given regulatory responsibility, that Center would oversee both the manufacture of the product and its resulting quality, but the other Center would not be precluded from participating in the oversight.¹⁷⁴ CDER was given the responsibility of regulating products from nonhuman animal, solid human tissue sources, chemically synthesized molecules (excluding vaccines or allergens), antibiotics, certain fungi and bacteria products, and hormone products.¹⁷⁵ CBER, in contrast, would regulate biological products that were subject to BLAs (such as vaccines, *in vivo* diagnostic allergenic products, human blood or immunoglobulin products, proteins, peptide or carbohydrate products), synthetically produced allergenic products, and certain drugs associated with blood banking.¹⁷⁶

For combination products that possessed both drug and biological components, the product would fall under CDER’s jurisdiction if the biological component “enhanced the efficacy or ameliorated the toxicity” of the drug component. A reverse result would place the product under CBER’s jurisdiction.¹⁷⁷ A combination product that contained a biological product coupled with either a radioactive component or a toxin component (that is not a drug) would be subject to CBER regulation, whereas a biological component that was

¹⁷² See CDER-CBER Intercenter Agreement, section III, *supra* n.95.

¹⁷³ *Id.*

¹⁷⁴ *Id.*

¹⁷⁵ *Id.* at section III.A.

¹⁷⁶ *Id.* at section III.B.

¹⁷⁷ *Id.* at section III.D.1.-2.

used to affect distribution of the product coupled with a nonradioactive drug component would be subject to CDER regulation.¹⁷⁸

One unique aspect of this Agreement was the designation of responsibility for medical reviews and pharmacology/toxicology reviews. Products approved by CDER and CBER implicate concerns for human health, safety, and exposure in a way that medical devices often do not. Thus, approval of the product by either Center would be conditioned upon the inclusion of an analysis of the product's effect in the fields of allergy, clinical immunology and rheumatology, hematology, oncology and infectious diseases.¹⁷⁹ Since multiple clinical subsets of each of those fields exist, the Agreement enumerated in more detail which Center would have primary medical review jurisdiction over each subset. Both Centers retained concurrent review jurisdiction over a third group of products, but the Center that would be assigned overall approval jurisdiction of the product was also responsible for the product's medical review.¹⁸⁰ If the medical review of a product was not delegated to the Center with the overall approval jurisdiction for that product (so-called "collaborative review"¹⁸¹), then both Centers would share the responsibility of completing the pharmacology/toxicology review.¹⁸² If CDER received approval jurisdiction for a product containing human source material, then CBER would be expected to consult on appropriate tests for unexpected agents within the product.¹⁸³ "Collaborative review" differed from a more informal consultation in that the Center with collaborative jurisdiction was bound to produce a definitive result from its review that would be included in the final administrative record, even if that Center did not have final product jurisdiction.¹⁸⁴

¹⁷⁸ *Id.*

¹⁷⁹ *Id.* at section IV.

¹⁸⁰ *See id.* at section IV.A.-C.

¹⁸¹ *See id.* at section VI.

¹⁸² *Id.* at section V.A.1.

¹⁸³ *Id.* at section V.B.

¹⁸⁴ *See id.* at section VI.

III.D. The Middle 1990's: The Continuing Effect of the SMDA

III.D.I. To Move or Not to Move the FDA Centers?

Following the passage of the SMDA and the promulgation of the corresponding regulations by the FDA, the recognition of combination products as a separate class deserving of separate regulatory procedures by the FDA took a quantum leap forward. Yet, once this change evolved into a common feature of the FDA's approval landscape, a familiar and still unresolved challenge rose once again for CDRH, CBER, and CDER: how actually to implement the statutory and administrative mandates that were set out for the Centers with three separate staffs that were increasingly inundated with premarket review requests and were physically separated in different FDA buildings.

At a hearing before the Subcommittee on Public Buildings and Economic Development of the House Committee on Transportation and Infrastructure, Commissioner of Food and Drugs, Dr. David A. Kessler, informed the Subcommittee that the FDA was still receiving an increasing number of requests for combination product premarket review.¹⁸⁵ More notably, his appearance before this particular Subcommittee was in conjunction with the FDA's campaign to consolidate its operations on two, as yet unapproved, centralized campuses in Maryland. According to Commissioner Kessler, "the current fragmentation of FDA review staff among many scattered facilities result[ed] in unnecessary approval delays for these [combination] products."¹⁸⁶ His support for consolidation of the FDA facilities was motivated in part by the same concerns that Senator

¹⁸⁵*Hearing Before the Subcomm. on Pub. Bldgs. and Econ. Dev. of the House Comm. on Transp. and Infrastructure*, 1995 WL 89247 (March 6, 1995) (statement of Dr. David A. Kessler, Commissioner, Food and Drug Administration). Commissioner Kessler also gave examples of some of the more recent applications for combination products, including "drug delivery systems, medicated wound dressing, bone cement containing an antibiotic, and dental composites with fluoride."

¹⁸⁶*Id.*

Kennedy expressed in promoting the SMDA five years earlier: “improvements in efficiencies” and continued improvement in “the time frames for product approval decisions.”¹⁸⁷

The administrative push for these two new FDA campuses, however, met with significant resistance from at least one source. C. Boyden Gray, the Chairman of Citizens for a Sound Economy, a non-profit research and education organization formed to advocate market-based solutions for public policy problems, testified before the Treasury, Postal Service, and General Government Subcommittee of the House Committee on Appropriations just two weeks after Commissioner Kessler made his statements in favor of the consolidated campuses.¹⁸⁸ Chairman Gray’s testimony focused upon the proposed expenditures for the two campuses, one of which would tentatively house CDRH, CBER, and CDER. He expressed skepticism at the FDA’s insistence that its “dispersed locations... have created both administrative and operations inefficiencies.”¹⁸⁹ In particular, he criticized the need for inter-Center communication by noting that “the number of products affected by more than one evaluating center is small compared to the total number of product applications evaluated by the agency each year. In all likelihood, an \$810 million campus will not significantly speed up the approval process for the relatively small number of products that need to be evaluated between centers.”¹⁹⁰ Instead, Chairman Gray advocated the continued use of the FDA’s state of the art, inter-agency computer network that allowed the premarket reviewers to communicate with each other via the World Wide Web.¹⁹¹

¹⁸⁷ *Id.*

¹⁸⁸ *Hearing Before the Subcomm. on Treasury, Postal Serv., and General Gov’t of the House Comm. on Appropriations*, 1995 WL 118134 (March 21, 1995) (statement of C. Boyden Gray, Chairman, Citizens for a Sound Economy).

¹⁸⁹ *Id.*

¹⁹⁰ *Id.*

¹⁹¹ *See id.*

The legislative record does not disclose an immediate response by the FDA, but the debate over the FDA campus consolidation continued. Fourteen months after Chairman Gray's claims that the consolidation of CBER, CDRH, and CDER into one building would be a waste of government spending, especially after the General Services Administration (GSA) was appropriated approximately \$325 million between 1992 and 1995 for the project,¹⁹² FDA Deputy Commissioner for External Affairs Sharon Smith Holston also addressed the Subcommittee on Public Buildings and Economic Development of the House Committee on Transportation and Infrastructure.¹⁹³ Her response to Chairman Gray was an appeal grounded in the experience of the FDA in the regulation of these products. She noted that

“[FDA’s] experience demonstrates that the Agency is increasingly required to resolve policy questions involving multiple FDA Centers, differing or overlapping statutory jurisdiction, or complex emerging developments in new science or technology that affect more than one of our Centers. This emerging trend means that there is a greater need for collaboration across Center lines, and for sharing resources, including personnel, equipment, and scientific expertise.... Consolidation will allow FDA scientists to engage in collaborative efforts that are critical both to the advancement of knowledge and to the coordination of research and review functions performed by the Agency.”¹⁹⁴

While Ms. Holston's comments did not disclose a radical development in FDA regulatory policy, they arguably indicated a frustration within the Agency that had continued unresolved five years after the passage of section 16 of the SMDA and four years after the corresponding premarket review regulations were published. Despite the Congressional efforts through the SMDA to provide for more efficient product regulation to further the public health, it appeared that the FDA was still struggling to realize the level of administrative efficiency and inter-Center informational collaboration that would need to exist before effective combination

¹⁹² *Id.*

¹⁹³ *Hearing Before the Subcomm. on Pub. Bldgs. and Econ. Dev. of the House Comm. on Transp. and Infrastructure*, 1996 WL 276588 (May 23, 1996) (statement of Sharon Smith Holston, Deputy Commissioner, Food and Drug Administration External Affairs).

product regulation could exist. The debate over the physical location of the three Centers only threw that continuing struggle into relief. Thus, the statutory recognition of combination products and the accompanying adjustments to the FDA's regulatory framework may have represented more of a quantum leap on paper than in practice.¹⁹⁵

III.D.2. The Biomaterials Access Assurance Act of 1996

Combination products continued to be implicated in unexpected ways throughout 1996, both in the debate over the FDA campus consolidation, and in the political battle over the legal limits of a medical device manufacturer's product liability in litigation. On March 14, 1996, a conference report was published on H.R. 956, the Common Sense Product Liability Legal Reform Act of 1996.¹⁹⁶ Title II of this Act contained the Biomaterials Access Assurance Act of 1996 ("BAAA").¹⁹⁷ The BAAA found that the suppliers of the raw materials and component parts used to make medical devices that are included later within combination products do not have a duty either to "evaluate the safety and efficacy of the use of a raw material or component part in a medical device" or to "warn consumers concerning the safety and effectiveness of a medical device."¹⁹⁸ Yet, to impose such a duty on those suppliers would "cause more harm than good

¹⁹⁵After all of the debate surrounding the consolidation of the FDA campuses, construction is currently underway on the White Oak campus in Montgomery County, Maryland. The consolidated campus is the result of explicit Congressional approval; in 1990, section 101 of the FDA Revitalization Act authorized the Secretary of Health and Human Services in conjunction with the Administrator of the General Services Administration (GSA) to begin contracting for a consolidated FDA facility. FDA Revitalization Act, Pub. L. No. 101-635, sec. 101, 104 Stat. 4583, 21 U.S.C. § 379b (November 28, 1990). Through the combined efforts of the GSA and the FDA, the new White Oak facility will finally house CBER, CDER, and CDRH in one location. The facility will provide updated laboratory space in addition to administrative office space for the FDA's research scientists and their support staff. The construction will be completed in yearly phases, with the CDER facilities to be completed first in 2007, the CDRH facilities to follow in 2008, and the CBER facilities to be finished in 2009. FDA Headquarters Consolidation at White Oak, at <http://www.fda.gov/oc/whiteoak/> (last visited April 16, 2004); FDA Headquarters Consolidation at White Oak Frequently Asked Questions, at <http://www.fda.gov/oc/whiteoak/faq.html> (last visited April 16, 2004).

¹⁹⁶H. REP. NO. 104-481, 142 Cong. Rec. H2238-05, 1996 WL 111996 (March 14, 1996).

¹⁹⁷Biomaterials Access Assurance Act of 1996 ("BAAA"), Pub. L. No. 105-230, 112 Stat. 1519, 21 U.S.C. §§ 1601 et seq. (August 13, 1998).

¹⁹⁸BAAA, § 202(13); 21 U.S.C. § 1601(13) (2004); 142 Cong. Rec. at H2242. Under the BAAA, a "medical device" includes

by driving the suppliers to cease supplying manufacturers of medical devices.”¹⁹⁹ Thus, to “safeguard the availability of a wide variety of lifesaving and life-enhancing medical devices” and device components of combination products, Congress determined that “immediate action [was] needed to clarify the permissible bases of liability for suppliers of raw materials and component parts for medical devices... and... to provide expeditious procedures to dispose of unwarranted suits against the suppliers in such manner as to minimize litigation costs.”²⁰⁰ The BAAA thus imposed product liability upon biomaterials suppliers for harm caused to a person by a medical implant, but only if that supplier was also the manufacturer or the seller of the implant.²⁰¹

While Congress sought to provide a legal defense from product liability to suppliers of raw materials or parts that are included in implantable medical devices, it distinguished the *device* parts from the other facets of a combination product, such as an active ingredient or drug.²⁰² By the terms of the BAAA, only the parts that qualified as medical devices were allowed to claim the legal defense, and not the parts provided by the suppliers or manufacturers of the active ingredient or drug. As the report stated, “this will ensure that the development and availability of such devices will not be impaired because of the same liability concerns affecting the availability of materials for other types of implants.”²⁰³ The BAAA stood as another example of how the advent of combination products had changed more than just the immediate regulatory landscape of the FDA. Congress found that a balance needed to be struck between the pressure felt by medical device

“any device component of any combination product as that term is used in section 503(g) of such Act (21 U.S.C. 353(g)).” BAAA, § 203(7); 142 Cong. Rec. at H2242.

¹⁹⁹BAAA, § 203(14); 142 Cong. Rec. at H2242. The BAAA, as enacted, did not employ the exact language of section 203(14). Rather, a similar provision was codified at 21 U.S.C. § 1601(8) that found that “even though suppliers of raw materials and component parts have very rarely been held liable in such actions, such suppliers have ceased supplying certain raw materials and component parts for use in medical devices for a number of reasons, including concerns about the costs of such litigation.”

²⁰⁰BAAA, § 202(15); 21 U.S.C. § 1601(15); 142 Cong. Rec. at H2242.

²⁰¹BAAA, §§ 205(a)(1), (b)(1), (c)(1); 21 U.S.C. §§ 1604(a)(1), (b)(1), (c)(1); 142 Cong. Rec. at H2243.

²⁰²See 142 Cong. Rec. at H2247.

²⁰³*Id.*

and combination product manufacturers to stay ahead of the technological curve and the safety of patients receiving those products. All of this legislation could be interpreted as an additional chapter in the pursuit of the original goal of the SMDA: to enable the financial and scientific growth of the combination product industry while preserving as preeminent the safety of the American public.

III.D.3. Up in Smoke: Combination Products and the Supreme Court

Before 1996 drew to a close, the FDA undoubtedly classified multiple new products as combination products. But one classification in particular, directed at a politically and culturally charged product, would become a fateful administrative decision. Never before had the FDA chosen to regulate tobacco products, but on August 28, 1996, the FDA chose to classify cigarettes as combination products. The nicotine constituted a drug while the cigarette and smokeless tobacco formed the “drug delivery device” to deliver the nicotine to the consumer.²⁰⁴ Defining tobacco products to be combination products as such meant that the FDA then had jurisdiction under the FDCA to investigate the labeling of the cigarette packages – labels that lacked claims of therapeutic benefits.²⁰⁵ More specifically, pursuant to its jurisdiction to regulate “restricted devices,”²⁰⁶ and its reasoning that the establishment of such jurisdiction would be necessary to provide a reasonable assurance of safety for cigarettes,²⁰⁷ the FDA promulgated regulations to change cigarette package labels. All cigarette labels would be required to contain the statement “A Nicotine-Delivery Device

²⁰⁴ See 61 Fed. Reg. 44396, 44397, 45208-16. (August 28, 1996). Nor did such a change in regulatory policy seem to be in conflict at the time that the Food and Drug Administration Modernization and Accountability Act of 1997 was being drafted. See 143 Cong. Rec. S8851-01, S8859, 1997 WL 545415 (September 4, 1997) (statement of Diane Duffy, Legislative Attorney, American Law Division to Senate Comm. on Labor and Human Resources).

²⁰⁵ *Id.* at 44402.

²⁰⁶ See 21 U.S.C. § 360j(e) (2004), which allows the agency to require that a device be restricted to sale, distribution, or use... upon such other conditions as [the FDA] may prescribe in such regulation, if, because of its potentiality for harmful effect or the collateral measures necessary to its use, [the FDA] determines that there cannot otherwise be reasonable assurance of its safety and effectiveness.

²⁰⁷ 61 Fed. Reg. at 44405-07.

for Persons 18 and Older” to prevent minors from smoking.²⁰⁸ Such a regulation was in accord with the FDA’s finding that if the number of children and adolescents who begin tobacco use can be substantially diminished, tobacco-related illness can be correspondingly reduced because data suggest that anyone who does not begin smoking in childhood or adolescence is unlikely ever to begin.²⁰⁹

In response, several tobacco manufacturers, advertisers and retailers filed suit in federal court against the FDA to challenge the labeling regulation.²¹⁰ They moved for summary judgment on three grounds: 1) that the FDA lacked the statutory jurisdiction to regulate cigarettes and smokeless tobacco as normally labeled, 2) that the FDA had exceeded its statutory authority under 21 U.S.C. § 360j(e) by attempting to regulate the advertisements and promotions of tobacco products, and 3) that such mandatory advertising restrictions violated the First Amendment. Although the District Court determined that the FDA had jurisdiction to regulate tobacco products pursuant to the FDCA,²¹¹ the court granted the motion in part on the ground that the mandatory advertising restrictions violated the FDA’s statutory grant under 21 U.S.C. § 360j(e), thus staying the promulgation of those regulations.²¹² The Court of Appeals for the Fourth Circuit split, but it reversed the District Court, finding that the FDA lacked the statutory authority to regulate tobacco products as they were normally marketed.²¹³ The Fourth Circuit found that Congress did not intend for the FDA to regulate tobacco products as combination products because, if the FDA had found cigarettes to be unsafe, they would have had to ban the product completely, rather than just requiring new product

²⁰⁸ *Id.* at 44615-18.

²⁰⁹ *Id.* at 44399.

²¹⁰ *See* *Coyne Beahm, Inc. v. FDA*, 966 F.Supp. 1374 (M.D.N.C. 1996).

²¹¹ *Id.* at 1388.

²¹² *Id.* at 1398-1401.

²¹³ *See* *Coyne Beahm, Inc. v. FDA*, 153 F.3d 155 (4th Cir. 1998). In his dissent, Judge K.K. Hall stressed that “the FDCA was broadly worded by design. In an area in which complex new products (and old products, seen in the light of new evidence) pose the potential for grievous harm, Congress deemed it necessary to delegate to an expert—the FDA—the job of monitoring drugs.” *Id.* at 182.

labels.²¹⁴ No legislative intent could be found to support the theory that the FDA should regulate tobacco products, and the court pointed out that the FDA itself had explicitly rejected the regulation of tobacco products through 1995.²¹⁵

The case was argued before the Supreme Court late in 1999. Four months later, the Supreme Court affirmed, 5-4, the Middle District of North Carolina and the Fourth Circuit's interpretation of the FDCA and the limits of the FDA's authority therein.²¹⁶ The FDA, like other federal agencies, are given wide latitude to interpret their statutory charge due to their specific administrative expertise, especially if Congress had not directly addressed the issue facing the agency.²¹⁷ But here, the Supreme Court found that the FDA's regulation of tobacco was inconsistent with the purpose of the provisions of the FDCA, including the combination product provision of 21 U.S.C. § 353(g)(1), and Congress' tobacco legislation following the passage of the FDCA. The FDA could not define a cigarette to be a "drug delivery device," find the device to be "unsafe" and "dangerous,"²¹⁸ but then subsequently allow it to remain on the market without violating the mandate of the FDCA to protect the public health.²¹⁹ The majority opinion conveyed an "all or nothing" understanding of the FDA's ability to regulate the manufacture and packaging of combination products.

Justice Breyer, in his dissent, construed 21 U.S.C. § 353(g)(1) in concert with 21 U.S.C. § 360j(e) in a different manner. He wrote:

²¹⁴ *Id.* at 164-67. The FDA is statutorily authorized to prevent products that are "unsafe" from reaching the market.

²¹⁵ *Id.* at 168-76. In his dissent, Judge Hall reminded the majority of the "familiar canon" of administrative law that allows an administrative agency to change its regulatory position, especially when new facts are discovered. *Id.* at 180 (citing *Rust v. Sullivan*, 500 U.S. 173, 186-87 (1991)).

²¹⁶ *See* *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2001).

²¹⁷ *See* *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984).

²¹⁸ *See* 61 Fed. Reg. at 44412.

²¹⁹ 467 U.S. at 135.

First, the [FDCA]’s language does not restrict the FDA’s remedial powers in this way. The FDCA permits the FDA to regulate a combination product—*i.e.*, a device (such as a cigarette) that contains a drug (such as nicotine)—under its device provisions. 21 U.S.C. § 353(g)(1). And the FDCA’s device provisions explicitly grant the FDA wide remedial discretion. For example, where the FDA cannot otherwise obtain reasonable assurance of a device’s safety and effectiveness, the agency may restrict by regulation a product’s sale, distribution, or use upon *such... conditions as the Secretary may prescribe*. § 360j(e)(1) (emphasis added). And the statutory section that most clearly addresses the FDA’s power to ban (entitled Banned devices) says that, where a device presents an unreasonable and substantial risk of illness or injury, the Secretary *may*—not *must*—initiate a proceeding... to make such device a banned device. § 360f(a) (emphasis added).²²⁰

As this excerpt illustrates, Justice Breyer focused upon the permissive language of the FDCA to construe the FDA’s authority to classify tobacco products as combination products broadly. The disagreement within the Court over the proper classification of cigarettes as “drug delivery devices” presented no statutory obstacle to Justice Breyer. To begin, the Court did not dispute that nicotine was properly classified as a drug. To further construe the cigarette as a device with which to convey the nicotine to the end user not only seemed appropriate to Justice Breyer, but justified given the purpose of the FDCA to protect the public health.²²¹ Such a classification provided the FDA with a variety of administrative actions regarding the sale of those restricted devices on the market. The FDA restricted the distribution of tobacco products to minors because the FDA could not obtain the necessary assurance that tobacco products were safe; § 360f(a) did not require the FDA to ban tobacco products completely. In other words, Justice Breyer found that the statutory framework provided by the FDCA allowed the FDA to provide adequate notice to consumers regarding the safety of cigarettes without requiring the FDA to completely remove an unsafe device from the market.²²²

²²¹Indeed, Justice Breyer began his dissent, *id.* at 161, by pointing out that the FDCA, when read literally, provided for the regulation of tobacco products because those products contained nicotine, an “article (other than food) intended to affect the structure or any function of the body.” 21 U.S.C. § 321(g)(1)(C). Second, the FDCA’s central purpose, to protect the public health, also argued for the inclusion of tobacco products within the FDA’s regulatory jurisdiction. *Id.* at 162; *see also* U.S. v. Article of Drug... Bacto-Unidisk, 394 U.S. 784, 798 (1969) (“FDCA is to be given a *liberal construction consistent with [its] overriding purpose to protect the public health* (emphasis added)). The majority disputed neither point in its opinion.

²²²*Id.*

Thus, the statute plainly allows the FDA to consider the relative, overall safety of a device in light of its regulatory alternatives, and where the FDA has chosen the least dangerous path, *i.e.*, the safest path, then it can—and does—provide a reasonable assurance of safety within the meaning of the statute. A good football helmet provides a reasonable assurance of safety for the player even if the sport itself is still dangerous. And the safest regulatory choice by definition offers a reasonable assurance of safety in a world where the other alternatives are yet more dangerous.²²³

Justice Breyer’s dissent arguably supports the goals behind the combination product provision of the SMDA, even though the majority favored a narrower construction of the FDCA with regards to public health and safety. The majority emphasized the importance of the public health, but it determined that the public health was constrained by its interpretation of the authority that Congress delegated to the FDA through the FDCA. Thus, “no matter how important, conspicuous, and controversial the issue, and regardless of how likely the public is to hold the Executive Branch politically accountable, *post*,... an administrative agency’s power to regulate in the public interest must always be grounded in a valid grant of authority from Congress.”²²⁴ Despite its *Chevron*-like recognition of the FDA’s expertise in regulating products that present a risk to the public health, the majority seemed to diverge from *Chevron*, a legally binding precedent, to focus upon Congress’ explicit delegation to the FDA and Congress’ subsequent, separate tobacco legislation.

Justice Breyer, in contrast, warned that the protection of the public health was not only a source of *Chevron*-like deference due to the FDA’s depth of expertise, but that it was in fact at the heart of the valid delegation made by Congress to the FDA when it enacted the FDCA. Thus, an action taken by the FDA to regulate a combination product that markedly implicated the public health, even though the FDA had explicitly rejected

²²⁴*Id.* at 161.

such regulation in the past, was properly within the statutory authority of the FDA.²²⁵ This interpretation supported the goal of the SMDA because section 16 of the SMDA made the FDA's initial regulation of tobacco products in 1996 possible and because the SMDA furthered the protection of the public health in part by providing more stringent and efficient regulation of combination products.²²⁶ More broadly, Justice Breyer construed Congress' delegation to the FDA through the general purpose of the FDCA and section 16 of the SMDA to allow the FDA to regulate combination products that implicated the public health as a means of efficiently consolidating within one administrative agency the *Chevron*-like expertise needed to best regulate such a product. This interpretation did not carry the day, however, and it appears the FDA thus may be limited to regulating as combination products, for example, those products that are more traditionally identifiable as a drug/device combination. Yet this litigation and Justice Breyer's dissent illustrated the impact that combination products have had on redefining the role of the FDA in protecting the public health today.

IV. Food and Drug Administration Modernization Act (FDAMA) of 1997

As the preceding section illustrated, the changes that the SMDA effected were felt beyond the statutory

²²⁵See *id.* at 163. Justice Breyer attached "no legal significance" to the FDA's regulatory change of heart, not only because controlling legal doctrine supported an administrative agency's change in policy, see *Chevron*, 467 U.S. at 863 (An initial agency interpretation is not instantly carved in stone), but because the FDA obtained evidence throughout the late 1980's and early 1990's that the tobacco companies knew of nicotine's addictive qualities, that the scientific evidence of the adverse health effects of tobacco use grew (see 61 Fed. Reg. 44701-06 (August 28, 1996)), and because the FDA regulatory policy simply changed with the advent of a new Administration and a new Commissioner. *Id.* at 188.

²²⁶In its decision to regulate tobacco products as combination products, the FDA applied 21 U.S.C. § 360j(e) to regulate tobacco products as restricted medical devices. Such a designation allowed the FDA to restrict the sale and distribution of tobacco products to persons over the age of 18 because the FDA could not be assured of the products' safety. See 21 U.S.C. § 360j(e)(1)(B); 61 Fed. Reg. 44,396, 44,400 (August 28, 1996). Thus, the FDA did not conclude that tobacco products were safe for human consumption by allowing their sale to the public.

prescriptions of the FDCA and the accompanying regulatory practice of the FDA. Still, improvements in the manner in which combination products were reviewed prior to their market release remained to be made. The Food and Drug Administration Modernization Act (FDAMA) of 1997, the next prominent round of amendments to the FDCA following the SMDA, did not amend the definition of a combination product or the substance of those provisions at 21 U.S.C. § 353(g). In full, FDAMA made very little mention of the regulation of combination products in general or in detail.

FDAMA did provide, however, a measure of autonomy to combination product manufacturers seeking regulatory approval for their new products. Section 416 of FDAMA, later codified at 21 U.S.C. § 360bbb-2 within the FDCA, allowed the manufacturer to request that its product be classified as a drug, biological product, device or combination product.²²⁷ In the alternative, section 416 allowed the manufacturer to request that a particular component of the product guide the decision as to which Center would regulate the product.²²⁸ In response, the FDA would provide its determination as to what product classification was appropriate or what component would guide the overall regulation of the product to the manufacturer within sixty days.²²⁹ If the FDA failed to make such a decision within sixty days, then the manufacturer's request would be considered the final determination of either the classification of the product or the component that guide the product's regulation.²³⁰ Such a final decision could not be changed unless the manufacturer agreed to the change in writing or new evidence arose that indicated that the product threatened the public safety.²³¹ Thus, FDAMA in its entirety did not effect sweeping changes in the regulation of combination products. Through a statutorily imposed time limit on the FDA's classification of each new product seeking approval,

²²⁷ 21 U.S.C. § 360bbb-2(a) (2004). *See also* Pub. L. No. 105-115, Title IV, sec. 416 (November 21, 1997).

²²⁸ *Id.*

²²⁹ 21 U.S.C. § 360bbb-2(b) (2004).

²³⁰ 21 U.S.C. § 360bbb-2(c) (2004).

²³¹ *Id.*

FDAMA did serve nonetheless to further the SMDA’s goal of an expedited, efficient regulatory process.

V. MDUFMA of 2002: The Advent of the Office of Combination Products

In 2001, the Executive Director of the Medical Device Manufacturers Association, Stephen Northrup, addressed the House Committee on Energy and Commerce to discuss the effects and shortcomings of FDAMA.²³² Specifically, Northrup believed that the SMDA and the FDAMA were only discrete steps on a continuous journey to keep the FDCA and the FDA’s practices current with technological progress. New and different combination products continued to arrive at the FDA’s doorstep²³³ such that the Center with primary premarket review jurisdiction often needed additional expertise from the other Centers. Northrup predicted that the evolution of these “hybrid” products would be such that their classification under one Center’s primary jurisdiction would become increasingly difficult.²³⁴

Northrup’s primary suggestion to ameliorate these problems would eventually prove visionary: he recommended an Office of Combination Products with “the authority to determine how a combination product will be reviewed and to coordinate all involvement by and interaction between the various FDA [C]enters in

²³²*Hearing Before the House Comm. on Energy and Commerce*, 2001 WL 475630 (May 3, 2001) (statement of Stephen Northrup, Executive Director, Medical Device Manufacturers Association).

²³³Northrup’s testimony cited a few of the latest examples of combination products coming from the medical device arena: drug-coated stents to fight restenosis, implanted drug-delivery pumps, artificial organs (such as livers, pancreases, and kidneys), nerve regenerators, and devices to provide genetic therapies. *Id.*

²³⁴*Id.* To illustrate this point, Northrup pointed to the Tissue Reference Group (TRG), initially established in 1998 by CBER and CDRH and comprised of three members of each Center. The TRG provided for device-biologic combination product manufacturers a single committee to draft guidance documents for these manufacturers and to answer their questions pertaining to approval jurisdiction and FDA regulations and policy.

the review of specific marketing applications.”²³⁵ With a goal reminiscent of Senator Kennedy’s comments during the debates over the SMDA, Northrup sought to encourage efficient use of the FDA’s resources, increase expertise within the FDA’s staff, and establish accountability for the agency’s actions. He testified that such an Office could efficiently operate with a small, “multi-disciplinary” staff that occasionally sought the additional input of experts from the three Centers. Further, Northrup believed that one Office would help to minimize the delays that still haunted the FDA review process for these “hybrid” products because of disagreements between the staff at different Centers, despite the Intercenter Agreements of 1991.²³⁶ An effective response to the appearance of these “hybrid” products that blurred the lines between drugs, devices, and biological products, in Northrup’s mind, was the creation of an Office that was equally hybridized in expertise and resources.

V.A. The First Step: The Combination Products Program

The FDA took the first step toward realizing Northrup’s vision when it created the Combination Products Program (hereinafter “CPP”) in February 2002.²³⁷ The program was established within the Office of the Ombudsman because the Ombudsman served as the product jurisdiction officer for combination products, designating which Center would have primary premarket review jurisdiction.²³⁸ The CPP was charged with “developing a number of initiatives to improve the review and regulation of combination products, including developing standard operating procedures to improve the management of the intercenter review process, monitoring the progress of premarket reviews of combination products, and developing guidance on a variety

²³⁵ *Id.*

²³⁶ *Id.*

²³⁷ See Regulation of Combination Products: FDA Employee Perspectives, at <http://www.fda.gov/oc/combination/perspectives.html> (last visited April 15, 2004). See also H. R. REP. NO. 107-728, at 39 (2002).

²³⁸ See 21 C.F.R. § 3.6 (1991) (designating Ombudsman as product jurisdiction officer pursuant to the SMDA).

of policy issues for combination products.”²³⁹ To determine the most pressing issues needing immediate resolution by the CPP and to formulate a future approach that would improve the efficiency of combination product review, approximately 25 reviewers (both premarket and postmarket) from all three Centers were interviewed by the CPP.²⁴⁰

Observations from the staff interviews, as well as the recommendations that were issued therein, were published by the FDA.²⁴¹ The interviews focused upon four key areas: consultation and collaboration between Centers, product jurisdiction, postmarket regulation issues, and electronic submission tracking systems. To summarize, the employees noted a lack of transparency within the Centers and stressed the need for continued intercommunication, education and “crosstraining” of combination product reviewers, especially since the employees believed that assigning combination product review only to experienced reviewers would enhance their efficiency and success in completing reviews. Due to time and resource constraints, reviewers often felt pressured to complete the review within one Center rather than spending time to obtain a consultation from another Center. Some reviewers were unsure even how appropriately to contact another Center. The Centers could not electronically track products within other Centers, nor electronically confer upon the status of that product. While the request for designation (RFD) procedures worked well generally, the employees noted that the Intercenter Agreements were outdated and in need of modernization because RFD procedures were employed rarely and “front-line reviewers” often shouldered the responsibility for determining if product

²³⁹ See Regulation of Combination Products: FDA Employee Perspectives, at <http://www.fda.gov/oc/combination/perspectives.html> (last visited April 15, 2004).

²⁴⁰ *Id.*

²⁴¹ *Id.* The findings by the CPP were extensive; in the name of brevity, only the most significant results are noted within this text. In addition to the posting of these findings and recommendations, the FDA also made available on its website a new, extensive Manual of Standard Operating Procedures and Policies (“SOPPs”) that would guide the “consultative and collaborative review process” between Centers when approving combination products. These SOPPs were originally approved on July 31, 2002 and have since been updated twice. See Intercenter Consultative/Collaborative Review Process, at <http://www.fda.gov/oc/combination/consultative.html> (last visited April 15, 2004).

jurisdiction was appropriate for their Center. Finally, when postmarket failures did occur, the Center with lead responsibility for such failure was not always apparent. The recommendations gleaned from the various Center employees focused upon keeping stakeholders informed of the changes within the FDA and the CPP, continuing the development of and monitoring of “review programs, policies, [and] processes,” creating transparent procedures that would be easily understood and followed by product manufacturers, and presenting the CPP as an advocate for the improved efficiency of combination product review.²⁴²

V.B. The Next Step: The Office of Combination Products

Nearly eighteen months later, both Houses of Congress were submerged in the final stages of sending a bill to the President that would, in part, incorporate Northrup’s suggestions. Originally sponsored by Representative James C. Greenwood and presented to the House pursuant to a report from the Committee on Energy and Commerce,²⁴³ H.R. 3580 made its way to the House floor for consideration on October 7, 2002.²⁴⁴ The bill was entitled “Medical Device User Fee and Modernization Act of 2002” (hereinafter “MDUFMA”) and it was drafted primarily to allow CDRH to charge fees to medical device manufacturers seeking market approval as a means of increasing both CDRH’s funding and its approval rate.

Section 203 of H.R. 3580, entitled “Designation and regulation of combination products,” was primarily written to address the concerns of the medical device industry, but the resulting provision had a broader scope. The most extensive Congressional statement with respect to the regulation of combination products

²⁴²*Id.*

²⁴³H. R. REP. NO. 107-728 (2002).

²⁴⁴H.R. 3580, 107th Cong., 148 Cong. Rec. H7153-03 (2002) (enacted).

since the passage of the SMDA, section 203, explicitly required the creation of an Office of Combination Products (hereinafter “OCP”).²⁴⁵ Not only did section 203 amend some of the language introduced by section 16 of the SMDA,²⁴⁶ it introduced the OCP, explained its mission, delineated the boundaries of its regulatory responsibility and provided for annual Congressional review of the performance of the OCP. The overall strategy of this provision was to deposit a layer of managerial responsibility and oversight, via the OCP, between the Commissioner’s office and the three Centers implicated by combination product review. In essence, the OCP would be charged with maintaining the delicate balance between an agency head charged with protecting the national public health and three technologically sophisticated Centers operating at the outer boundaries of innovation.

To that end, paragraphs (4)(A)-(C) gave the OCP the authority to assign primary premarket approval jurisdiction to one Center,²⁴⁷ with the possibility of consultation from the Office of the Commissioner,²⁴⁸ while “overseeing and coordinating reviews” that involved multiple Centers.²⁴⁹ Yet this section also barred the OCP from preempting the *postmarket* regulatory authority of any of those Centers.²⁵⁰ Each Center, in return, would be responsible to the OCP for the timeliness of its product approvals²⁵¹ and if a dispute arose regarding the rate at which that Center generated approvals, those disputes would be resolved by the

²⁴⁵ *Id.* at H7158.

²⁴⁶ *See supra* n.112. The amendments to, and not the additions to, the preexisting language of section 16 of the SMDA, 21 U.S.C. § 353(g), by section 203 of H.R. 3580 were necessary to create future statutory agreement between the two amendments to the FDCA. The modified language, however, was not revolutionary. Rather, the language modifications simply provided that “Section 503(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(g)) is amended-

(1) in paragraph (1) -

(A) in the first sentence, by striking shall designate a component of the Food and Drug Administration and inserting shall in accordance with this subsection assign an agency center; and

(B) in each of subparagraphs (A) through (C), by striking the persons charged and inserting the agency center charged;

(2) by redesignating paragraph (4) as paragraph (5)...” 148 Cong. Rec. at H7158.

²⁴⁷ H.R. 3580, 107th Cong., § 203(4)(B) (2002).

²⁴⁸ *Id.* at § 203(4)(A).

²⁴⁹ *Id.* at § 203(4)(C).

²⁵⁰ *Id.* at § 203(4)(D) (emphasis added).

²⁵¹ *Id.* at § 203(E).

OCP.²⁵² Disputes over more substantive matters, however, such as the claims within the manufacturer's market application that could not be resolved by the lead Center would be forwarded to the Office of the Commissioner for resolution that could then request input from the OCP.²⁵³ Section 203 also called for a review of the prior agreements and guidance documents that had been generated by the FDA with regard to the regulation of combination products. That review was to engage the input of each Center's director. If such agreements or documents needed modification, reapproval, or elimination, FDA was charged with fulfilling that duty.²⁵⁴ Finally, the section that gave birth to the OCP required an annual report with Congress on the progress of the OCP to date. More specifically, the report would include "provisions (i) describing the numbers and types of combination products under review and the timeliness in days of such assignments, reviews, and dispute resolutions; (ii) identifying the number of premarket reviews of such products that involved a consulting agency center; and (iii) describing improvements in the consistency of postmarket regulation of combination products."²⁵⁵

When the report accompanying H.R. 3580 was submitted to the House on October 7, 2002, the legislation had yet to be debated. No hearings were held before the Committee on Energy and Commerce prior to the presentation of the report.²⁵⁶ The Committee stressed that the Office of the Ombudsman (within the Office of the Commissioner) would still make the initial determination as to whether a product was indeed a combination product, but that the Ombudsman could consult with the OCP if necessary to determine the product's initial classification. The report also made clear that section 203 would continue the administrative

²⁵² *Id.* at § 203(F)(i).

²⁵³ *Id.* at § 203(F)(ii).

²⁵⁴ *Id.* at § 203(G).

²⁵⁵ *Id.* at § 203(H).

²⁵⁶ H.R. REP. NO. 107-728, at 21 (2002).

procedure that was originally introduced as the “primary mode of action” determination in the SMDA.²⁵⁷ The section would still permit a manufacturer to submit its application to the Center that it deemed most appropriate to retain lead approval jurisdiction.²⁵⁸ In all, the Committee’s report indicated that section 203 was aimed mostly at improving the “timeliness” of the premarket approval process of combination products. Disputes that arose that could not be managed solely within the Center with primary jurisdiction could be addressed to the Office of the Commissioner, but as a last resort. Rather, as the report stated, “[t]he Committee does not intend for the new Office to be micro-managing line reviewers within the different Agency Centers. The bill instead contemplates that, with respect to the timeliness of reviews, the Centers themselves will be responsible to the new Office.”²⁵⁹

An addendum to the Committee on Energy and Commerce’s report was presented to the House on October 15, 2002. The addendum contained the estimated cost (as prepared by the Congressional Budget Office, or CBO) of enacting H.R. 3580.²⁶⁰ In all, the CBO determined that H.R. 3580 itself would cost \$36 million to implement between 2003 and 2007, at which point the provisions would “sunset,” or no longer be enforceable, if unsuccessful.²⁶¹ This estimate, however, did not provide the full picture. For example, the CBO also estimated that the user fee program would require an additional \$78 million in Congressional appropriations during the same time period to prevent early termination of the user fee program.²⁶² By sharp contrast, the CBO estimated that the OCP would require \$1 million in appropriations for the 2003

²⁵⁷ *Id.* at 39.

²⁵⁸ *Id.* at 39-40.

²⁵⁹ *Id.*

²⁶⁰ H.R. REP. NO. 107-728(II) (2002). As the report addendum explained, “CBO assumes that the bill will be enacted in the fall of 2002 and that outlays will follow historical spending rates for the authorized activities. Where H.R. 3580 specifies the amounts authorized to be appropriated, CBO assumes that such appropriations will be made. Where appropriations of such sums as necessary are authorized, CBO assumes that the estimated amounts will be provided for each fiscal year.” *Id.* at 3.

²⁶¹ *Id.* at 2.

²⁶² *Id.*

fiscal spending year and that an additional \$4 million would allow the OCP to operate through 2007.²⁶³ The first year of operation for the OCP would be more expensive than the following three years, the CBO estimated, because more staff would be needed to update data with regards to product tracking and to establish operating procedures for the OCP.²⁶⁴

The debate on the House floor that followed the presentation of the Committee's initial report was not extensive, but was definitively supportive of section 203.²⁶⁵ Representative Eshoo noted that the provision would help to “shepherd” combination products through the approval process, thereby allowing the FDA to focus upon approving the medical devices that patients needed most.²⁶⁶ Representative Greenwood, H.R. 3580's sponsor, also echoed this theme of efficiency and protection of the public by pointing out that section 203 would eliminate the “regulatory logjams” that the FDA faced while ensuring that combination products were properly classified and assigned.²⁶⁷ In a unique extension of remarks on the House floor, Representative Mark E. Souder of Indiana expressed his approval of the passage of H.R. 3580 because Kosciusko County in Northern Indiana was one of the nation's leading sites for production of medical devices.²⁶⁸ He highlighted the streamlined approval procedures that the OCP would provide for product manufacturers while noting that “this expedited procedure will not sacrifice thoroughness for speed. This legislation carefully spells out strict standards to ensure the absolute highest level of safety.”²⁶⁹

²⁶³ *Id.* at 6.

²⁶⁴ *Id.*

²⁶⁵ 148 Cong. Rec. at H7162.

²⁶⁶ *Id.*

²⁶⁷ *Id.* at H7163.

²⁶⁸ 148 Cong. Rec. E1844 (2002).

²⁶⁹ *Id.*

A little more than one week later, the House was again asked by the Committee on Energy and Commerce to consider the MDUFMA, but in another form. H.R. 3580 had been abandoned, or more properly, amended such that H.R. 5651 was now the legislation seeking passage.²⁷⁰ In fact, section 203 became section 204 within H.R. 5651 because the Committee drafted a new provision as section 203: the debarment of accredited third-party reviewers of premarket product applications.²⁷¹ Section 204 in particular was amended, it could be argued, more fully to incorporate Rep. Greenwood's theme of timeliness and efficiency of review. Since section 204 of H.R. 5651 was the final provision allowing for the creation of the OCP as enacted by Congress and signed by the President, the full text of this noteworthy legislative development is included here:

²⁷⁰H.R. RES. 5651, 107th Cong., 148 Cong. Rec. H7964 (2002) (enacted) (introduced by Rep. Arney).

²⁷¹*Id.* at § 203.

SEC. 204. DESIGNATION AND REGULATION OF COMBINATION PRODUCTS.

Section 503(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(g)) is amended-

(1) in paragraph (1) -

(A) in the first sentence, by striking shall designate a component of the Food and Drug Administration and inserting shall in accordance with this subsection assign an agency center; and

(B) in each of subparagraphs (A) through (C), by striking the persons charged and inserting the agency center charged;

(2) by redesignating paragraph (4) as paragraph (5);

(3) by inserting after paragraph (3) the following paragraph:

(4)(A) Not later than 60 days after the date of the enactment of this paragraph, the Secretary shall establish within the Office of the Commissioner of Food and Drugs an office to ensure the prompt assignment of combination products to agency centers, *the timely and effective* premarket review of such products, and consistent and appropriate postmarket regulation of like products subject to the same statutory requirements to the extent permitted by law. Additionally, the office shall, in determining whether a product is to be designated a combination product, consult with the component within the Office of the Commissioner of Food and Drugs that is responsible for such determinations. Such office (referred to in this paragraph as the 'Office') shall have appropriate scientific and medical expertise, and shall be headed by a director.

(B) In carrying out this subsection, the Office shall, for each combination product, promptly assign an agency center with primary jurisdiction in accordance with paragraph (1) for the premarket review of such product.

(C)(i) In carrying out this subsection, the Office shall ensure timely and effective premarket reviews by overseeing the timeliness of and coordinating reviews involving more than one agency center.

(ii) In order to ensure the timeliness of the premarket review of a combination product, the agency center with primary jurisdiction for the product, and the consulting agency center, shall be responsible to the Office with respect to the timeliness of the premarket review.

(D) In carrying out this subsection, the Office shall ensure the consistency and appropriateness of postmarket regulation of like products subject to the same statutory requirements to the extent permitted by law.

(E)(i) Any dispute regarding the timeliness of the premarket review of a combination product may be presented to the Office for resolution, unless the dispute is clearly premature.

(ii) During the review process, any dispute regarding the substance of the premarket review may be presented to the Commissioner of Food and Drugs after first being considered by the agency center with primary jurisdiction of the premarket review, under the scientific dispute resolution procedures for such center. The Commissioner of Food and Drugs shall consult with the Director of the Office in resolving the substantive dispute.

(F) The Secretary, acting through the Office, shall review each agreement, guidance, or practice of the Secretary that is specific to the assignment of combination products to agency⁶⁰ centers and shall determine whether the agreement, guidance, or practice is consistent with the requirements of this subsection. In carrying out such review, the Secretary shall consult with stakeholders and the directors of the agency centers. After such consultation, the Secretary shall determine whether to continue in effect, modify, revise, or eliminate such agreement, guidance, or practice, and shall publish in the Federal Register a notice of the availability of such modified or revised agreement, guidance or practice. Nothing in this paragraph shall

The amendments to section 203 of H.R. 3580 that appear within section 204 of H.R. 5651 above have been italicized to illustrate the thematic changes in agreement with Rep. Greenwood’s position. Paragraph (4)(A), that originally called for the “timely” premarket review of combination products, now mandated their “timely and effective” premarket review.²⁷³ Paragraph (4)(C) within H.R. 3580 became paragraph (4)(C)(i) within H.R. 5651, and the word “overseeing” as it related to reviews was modified to read “overseeing the timeliness of ...” instead.²⁷⁴ Paragraph (4)(E) within H.R. 3580 became paragraph (4)(C)(ii) within H.R. 5651, and the last sentence of paragraph (4)(D) within H.R. 3580 became paragraph (4)(H) within H.R. 5651.

Of note within paragraph (4)(H), however, is the removal of the word “postmarket” from the phrase “regulatory authority.”²⁷⁵ With this amendment, section 204(4)(H) would seem to have narrowed the role of the new OCP before it was even statutorily created. It is arguable that this amendment occurred because the Committee intended the OCP to occupy a uniquely supervisory role over the smooth functioning and intercommunication of the three Centers rather than conducting the premarket approval review of combination products itself. Each of the three Centers would still complete the premarket approval of the products appropriately classified to them, using the same staff and same approval procedures as in the past, while the OCP monitored their progress and collaboration. Thus, it was appropriate, if not necessary, to vest continued regulatory authority in each Center (notably the Center with primary jurisdiction for combination products) because that Center would be directly responsible for its decision to the OCP pursuant to § 204(4)(C)(ii).

²⁷³ *Id.* at § 204(4)(A).

²⁷⁴ *Id.* at § 204(4)(C)(i).

²⁷⁵ *Id.* at § 204(4)(H). *See supra* n.250.

The amended responsibilities of the OCP within section 204 of H.R. 5651 were passed by the House on October 16, 2002.²⁷⁶ The following day, the Senate continued the debate surrounding these provisions in anticipation of its own vote.²⁷⁷ As Senator Kennedy pointed out, “We have been working on this legislation for 10 years. It has been a divisive issue, both the issue and as a public policy issue... I indicate [that] this is a public health matter of enormous importance and consequence.”²⁷⁸ The bill passed in the Senate that day as well, indicating the universal approval for the provisions that would amend the FDCA and “bring FDA regulation into the 21st century.”²⁷⁹ H.R. 5651 was presented to President George W. Bush on October 25, 2002²⁸⁰ and the Medical Device User Fee and Modernization Act of 2002 became law on October 26, 2002.²⁸¹

VI. *The Current Status of the Office of Combination Products*

With the President’s signing of the MDUFMA on October 26, 2002, the OCP became a statutory responsibility of the FDA. There was no doubt that its advent was overdue. FDA stakeholders reported that the number of new combination products seeking premarket approval was expected to continue to increase.²⁸²

²⁷⁶148 Cong. Rec. at H7964-65.

²⁷⁷148 Cong. Rec. S10752 (October 17, 2002).

²⁷⁸148 Cong. Rec. at S10619. Perhaps in a more pointed display of his support for H.R. 5651, Senator Kennedy proceeded, “If Members are going to object, they are going to have to come to the floor of the Senate and express those objections and reasons. We will not tolerate someone holding up this bill in hopes that they can get it carried back to the House.” *Id.*

²⁷⁹148 Cong. Rec. at 10754 (statement by Sen. Gregg).

²⁸⁰148 Cong. Rec. H8043 (October 28, 2002).

²⁸¹*See supra* n.2.

²⁸²*See* Overview of the Office of Combination Products, at <http://www.fda.gov/oc/combination/overview.html> (last visited April 15, 2004).

Recent examples of such sophisticated products include a glucose meter that integrated an insulin pump with a dose calculator,²⁸³ dermal collagen implants for aesthetic use,²⁸⁴ and a drug-eluting stent used to unclog heart arteries.²⁸⁵ Congress provided the OCP with a broad statutory grant to oversee the entire “regulatory life cycle” of a combination product, from assigning the product to one Center with primary review jurisdiction, to coordinating a timely and effective premarket review process when the product required input from multiple Centers, to providing uniform postmarket procedures. In addition, the OCP would be expected to resolve intercenter disputes arising over the proper review procedures to be applied by helping to guide and reformulate the procedures themselves. Finally, such decisions as the OCP made would be subject to annual Congressional review.²⁸⁶

VI.A. The First Public Hearing

Despite these broad mandates, the unavoidable challenge for the FDA still came in making the OCP a reality. The discussion, *supra*, of the findings and recommendations of the CPP, gleaned from the perspectives of Center employees, illustrated a multilayered problem of intercommunication breakdowns, outdated procedures used by a staff that was limited in time and resources, and a lack of crosstraining between Centers for different types of combination products. Thus, the FDA approached the incorporation of the OCP into the Office of the Commissioner in a methodical, stepwise fashion. At base, confusion surrounding and concerns about the manner in which the Centers within the FDA should be regulating combination products day

²⁸³See FDA Clears New Diabetes Device for Marketing, at <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00918.html> (last visited April 15, 2004).

²⁸⁴See CosmoDermTM 1 Human-Based Collagen, CosmoDermTM 2 Human-Based Collagen, and CosmoPlastTM Human-Based Collagen P800022S050, at <http://www.fda.gov/cdrh/pdf/p800022S050.html> (last visited April 15, 2004).

²⁸⁵See FDA Approves Drug-Eluting Stent for Clogged Heart Arteries, at <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00896.html> (last visited April 15, 2004). For more examples of recently approved combination products, see Recent Examples of Combination Product Approvals, at <http://www.fda.gov/oc/combo/combination/approvals.html> (last visited April 15, 2004).

²⁸⁶*Id.*

to day would need resolution before the FDA could establish the OCP to oversee the subsequent, smooth intercommunication between the Centers.

Although the Commissioner of Food and Drugs approved a press release about the new OCP on December 31, 2002,²⁸⁷ the FDA published a notice in the Federal Register just two days after the passage of the MDUFMA to invite public comment at a hearing on November 25, 2002 with regards to the “assignment, premarket review, and postmarket regulation of combination products.”²⁸⁸ Within this notice, there was no mention of the OCP, but rather the notice cited the CPP within the Office of the Ombudsman.²⁸⁹ That omission, however, may have been either the result of a public notice that had been drafted for the Federal Register prior to the passage of the MDUFMA or an implicit recognition that, once the MDUFMA was enacted, the OCP would assume formally the duties of the CPP.²⁹⁰ What the notice did allude to, however, were the concerns that product manufacturers had about the lack of clarity, efficiency, and predictability of the FDA’s combination product approval mechanisms.²⁹¹ To that end, the FDA requested that organizations interested in commenting on the current status of combination product review answer a variety of questions ranging from the flexibility of the Intercenter Agreements to the definition of “primary mode of action” to whether a product should be subject to one or more applications for premarket approval.²⁹²

²⁸⁷ See *supra* n.1.

²⁸⁸ 67 Fed. Reg. 65801 (October 28, 2002).

²⁸⁹ See *supra* n.237.

²⁹⁰ See H. R. REP. NO. 107-728, at 39 (2002) (expressing the Committee’s intent that the OCP would continue the efforts of the CPP). See also Overview of the Office of Combination Products, at <http://www.fda.gov/oc/combination/overview.html> (last visited April 15, 2004) (noting that “The Office also has assumed the functions of the Combination Products Program begun in 2002 within the FDA Office of the Ombudsman. Among these functions [are] working with FDA Centers to develop guidance or regulations to clarify the agency regulation of combination products [and] serving as a focal point for combination products issues for internal and external stakeholders.”)

²⁹¹ *Id.* at 65802.

²⁹² *Id.* at 65803.

Attendees at the public hearing represented a wide variety of professional backgrounds and regulatory interests. Physicians, laboratory researchers, attorneys and manufacturing executives all weighed in with their impressions of how the future of combination product review should be shaped.²⁹³ One of the FDA panelists overseeing the hearing was Dr. Mark Kramer, Director of the Combination Products Program within the Ombudsman's Office. At least one participant noted that the outcome of this hearing was, in part, necessary to guide the immediate future of the OCP.²⁹⁴

While many of the speakers encouraged the FDA to increase its efficiency and oversight procedures in general terms,²⁹⁵ a few participants made noteworthy suggestions. Dr. Barbara D. Boyan, Ph.D., who spoke on behalf of the American Academy of Orthopaedic Surgeons, advocated for a "multidisciplinary" approach,²⁹⁶ in which a team of physicians, scientists, and engineers would work cooperatively to review a combination product from the time that the product application is submitted to its final approval. She also proposed that the "primary mode of action" of a product include its method of use.²⁹⁷ Ultimately, Dr. Boyan, and many of the other speakers at the hearing, strongly urged the FDA to limit the review process to one application for each combination product.²⁹⁸

Continuing a previous theme, Dr. Paul Goldfarb, M.D., who represented Genetronics, Inc., encouraged the

²⁹³Transcript of the Public Hearing on November 25, 2002 on FDA Regulation of Combination Products, at <http://www.fda.gov/oc/combination/transcript112502.html> (last visited April 11, 2004).

²⁹⁴*Id.* (statement of Dr. Murray Lumpkin, FDA Principal Associate Commissioner).

²⁹⁵*Id.* (*see, e.g.*, statement of Dr. Owen Fields, Ph.D., Regulatory Affairs, Wyeth Pharmaceuticals).

²⁹⁶*Id.* Dr. Fields referred to this as an "intercenter review team."

²⁹⁷*Id.* Ms. Ashley Whitesides, Esq., King & Spaulding, concurred that those products that were intended for identical uses should be categorized together and primarily regulated by the same Center.

²⁹⁸*Id.* Other speakers, however, argued that certain combinations contain two or more components that are diverse enough to require separate approval applications. One example of such a product was a magnetic resonance system, where the drug that provided the imaging effect, never physically contacted the device.

FDA to consider the primary mode of action from the patient’s perspective.²⁹⁹ Dr. Goldfarb, in conjunction with Dr. Fields and a few other speakers, believed that the therapeutic effect of the product should weigh heavily in the determination of the primary mode of action.³⁰⁰ Such an interpretation would continue the historical approach of the FDA in determining the primary mode of action and building the OCP’s approach from that point.³⁰¹ Another expert argued that premarket approval lead jurisdiction should be granted to the Center best equipped to assess the product’s risk and to assure the safety of the product to patients.³⁰² Finally, Dr. Stuart Portnoy, M.D., formerly a FDA Branch Chief of the Interventional Cardiology Devices Branch, voiced a unique position when he argued that “it is essential for the reviewers of combination products to continue to work from within their respective centers, and not be pulled out to populate this new office.”³⁰³ He believed that the product reviewers within each Center would only maintain their specific expertise if they stayed within those Centers. Thus, the “cross-center review teams” should not be abandoned in favor of the “multidisciplinary” approach advanced by Dr. Boyan and the OCP should occupy the role intended for it by Congress: administrator of FDA inter-Center communication.³⁰⁴

From this hearing, the FDA promulgated a final ruling, published in the Federal Register on June 23, 2003.³⁰⁵

²⁹⁹ *Id.*

³⁰⁰ *Id.* Mr. Michael Gross, Vice President of Worldwide Compliance for Aventis Behring, a biologics manufacturer, agreed.

³⁰¹ *Id.* (statement of David Fox, Esq., Hogan & Hartson, LLP). Mr. Fox disagreed that multiple applications presented an efficiency problem for combination product review as the intercommunication and coordination between Centers had increased. Ms. Patricia Shrader, Esq., Corporate Vice President of Regulatory Affairs and Compliance at Becton, Dickinson and the company spokesperson of AdvaMed, which is the largest medical technology association in the world, agreed that the historical approach to determining the primary mode of action was the most appropriate approach. Her position, however, was predicated upon an argument based in industrial and administrative inertia that thousands of manufacturers had come to rely upon the historical definition of the primary mode of action in filing their own applications, such that a change at this time would create unnecessary confusion.

³⁰² *Id.* (statement of Dr. Guy Chamberland, Ph.D., Vice President of Regulatory Affairs and Drug Development, Angiogene, Inc.). Dr. Fields proposed a similar idea, as did Dr. Zorina Pitkin, Ph.D., Vice President of Regulatory Affairs and Quality Systems at Nephros Therapeutics, Inc. Mr. Fox, by contrast, largely discounted this consideration because any Center at FDA could provide the appropriate safety and effectiveness information, regardless of whether the Center had primary review jurisdiction.

³⁰³ *Id.*

³⁰⁴ *Id.*

³⁰⁵ 68 Fed. Reg. 37075-01 (June 23, 2003).

The ruling explained how some of the regulations that had been promulgated as the result of the passage of the SMDA, 21 C.F.R. §§ 3.1 et seq., would require further amendment as a result of the MDUFMA. Those changes, however, were mostly superficial. The major suggestions advanced by many of the speakers at the public hearing were not incorporated into the OCP's formal regulatory framework. Section 3.1, the statement of purpose behind these combination product regulations, was modified to cite the MDUFMA as one source of authority for the combination product regulations.³⁰⁶ Section 3.2 was amended to make the definitions of "agency component" and "agency center," (as both were used within the FDCA) compatible, and section 3.6 was revised to cite the OCP as the combination product jurisdiction officer, rather than the Ombudsman.³⁰⁷ Designating the OCP as the new product jurisdiction officer meant that the OCP would now make the original determination as to which Center would have primary premarket review responsibility for combination products and for products whose review jurisdiction was in dispute.³⁰⁸ Sections 3.7 and 3.9 were also modified in minor ways to correlate with the FDA's current organizational structure.³⁰⁹

VI.B. The First Six Months

Between the public hearing in November 2002 and the issuance of the final rule that modified the OCP's governing regulations, the OCP issued two quarterly progress reports to its stakeholders.³¹⁰ The first report explicitly stated that the OCP was focusing on establishing procedures in furtherance of its statutory

³⁰⁶21 C.F.R. § 3.1 (2003); 68 Fed. Reg. at 37077.

³⁰⁷21 C.F.R. §§ 3.2, 3.6 (2003); 68 Fed. Reg. at 37077.

³⁰⁸See *Assignment of Combination Products/Product Jurisdiction Program*, at <http://www.fda.gov/oc/combination/assignment.html> (last visited April 16, 2004). See also *Overview of the Office of Combination Products*, at <http://www.fda.gov/oc/combination/overview.html> (last visited April 16, 2004).

³⁰⁹21 C.F.R. §§ 3.7, 3.9 (2003); 68 Fed. Reg. at 37077.

³¹⁰First Quarterly Progress Report to Stakeholders, January – March 2003 ("First Quarterly Report"), at <http://www.fda.gov/oc/combination/firstquarter2003.html> (last visited April 15, 2004). Second Quarterly Progress Report to Stakeholders, April – June 2003 ("Second Quarterly Report"), at <http://www.fda.gov/oc/combination/secondquarter2003.html> (last visited April 15, 2004).

responsibilities; to that end, it highlighted in a succinct fashion its actions during its first three months of existence. During the first three months of 2003, the OCP received six requests for product assignment and issued four of those assignments. Of those four assignments, all of them were issued within sixty days of the OCP's receipt of the request; the average review time was 37 days³¹¹ Two products were primarily assigned to CBER, and one of each of the remaining products was assigned to CDER and CDRH.

In addition to this statistical data, the OCP stated that it was working to adapt the definition of “primary mode of action,” probably in response to the statements at the public hearing, and that proposed definitions were being used in test cases.³¹² A new “internal precedent documentation system” was established to allow each Center to retroactively catalog old assignment decisions and to refer to prior relevant precedents when confronted with a new application.³¹³ More importantly, the OCP developed an electronic, web-based database that would allow the Centers to track the progress of each consultation request made on a combination product. The OCP also revised the SOPPs of the Intercenter Consultative/Collaborative Review Process³¹⁴ utilized by the Centers to complement the use of the electronic database. Not forgetting that the OCP was charged with overseeing the “entire regulatory cycle” of combination products, new working groups were formed within the OCP to create guidance documents that would inform manufacturers in advance of the role that the Centers expected to play in continuing *postmarket* monitoring of specific combination products. The report noted that CDRH and CDER especially would be implicated by this new procedure because they anticipated a marked increase in a specific category of combination product that would require this monitoring in the future. In essence, the first quarterly progress report captured the OCP at a “feet-

³¹¹ See First Quarterly Report, *supra* n.310.

³¹² *Id.*

³¹³ *Id.*

³¹⁴ See *supra* n.241.

wetting” stage, as it began its oversight responsibilities through meetings with various groups of stakeholders and debriefings with the staff of Center review teams, and as it responded to inquiries fielded by both FDA staff and product manufacturers.³¹⁵

One particularly innovative approach that was tentatively adopted by the OCP was cited briefly in the report. Section 204 of the MDUFMA charged the OCP with the “timely and effective” premarket review of combination products.³¹⁶ The OCP noted that two Centers interacted often enough on a range of combination products that a “two-Center, two-application collaborative premarket review” could provide a more appropriate and efficient means of reviewing a new combination product without minimizing each Center’s input or expertise. After one such collaborative team had completed a premarket review with this new application, the OCP debriefed the other Center review teams and planned to debrief the manufacturer later on the results of the trial inter-Center collaboration. The OCP hoped that the feedback that was generated by the test review team would help it to generate tools to use in further collaborative premarket reviews with other teams.³¹⁷

Another noteworthy choice disclosed in the first quarterly report was the balancing act that the infant OCP undertook. Many of the steps taken immediately following the enactment of the MDUFMA by the OCP were directed at modernizing current regulatory practices by the Centers and facilitating their intercommunication. Yet the report also disclosed that the OCP jumped headlong into breaking new administrative ground.

³¹⁵See First Quarterly Report, *supra* n.310.

³¹⁶See *supra* n.272.

³¹⁷See First Quarterly Report, *supra* n.310. This inter-Center, team-oriented or “multidisciplinary” approach also was advocated for by some of the speakers at the public hearing. See *supra* n.296.

Working groups were established to “clarify and develop the regulatory pathways for novel drug delivery systems and drug/test kit combination products based on pharmacogenomics. OCP [was] also participating in the working groups being established to develop guidance documents for products for diabetes and obesity.”³¹⁸ These steps were part of the “Commissioner’s Technology Development Initiatives.”³¹⁹ Such an assertive move, to resolve old problems while simultaneously laying the groundwork to regulate cutting-edge technology, revealed an experienced sophistication and dedication that belied the brand-new veneer of the OCP.

The second quarterly progress report provided to stakeholders also drew a concise, yet illustrative, picture of the continuing evolution of the OCP.³²⁰ Product jurisdiction reviews were finally consolidated within the OCP, completing the transfer from the Office of the Ombudsman. The OCP promulgated the final rule in the Federal Register on June 23, 2003.³²¹ As expected, the OCP continued to oversee and facilitate inter-Center communication. It accomplished this, in part, by completing a retrospective analysis of consultative reviews completed during the first six months of 2003. Regulatory challenges that still needed resolution included whether an updated definition of the “primary mode of action” was necessary and whether a single product application or separate applications, managed by inter-Center review teams, more effectively furthered the OCP’s responsibility to approve combination products in a “timely and effective” way. As before, the OCP forged ahead with creating regulatory pathways for new combination products and establishing a new working group to consider whether cross-labeling of some combination products was feasible.³²² Postmarket review

³¹⁸ See First Quarterly Report, *supra* n.310.

³¹⁹ *Id.*

³²⁰ See Second Quarterly Report, *supra* n.310.

³²¹ See *supra* n.305.

³²² Although no example is provided, cross-labeling issues may arise when a combination product consists of two physically distinct components that are intended for concomitant use. See, e.g., *supra* n.133, 298.

factors, such as adverse events, good manufacturing practices, and the registration of approved combination products, were elucidated further by OCP working groups. Physically, the OCP consolidated itself into one location, added and trained new staff, and continued to expand its website by providing links to guidance documents and examples of recently approved combination products.

In fact, many of the changes brought about by the OCP in the second quarter dealt with enhancing its electronic capabilities. The internal request for designation (RFD) database that contained prior approval precedents continued to be updated, as was the web-enabled database that allowed each of the Centers to track, monitor, and complete consultation requests between Centers.³²³ Work began on an OCP “intranet” site that would allow OCP staff to access all the pertinent information related to the regulation of combination products. An “algorithm and categorization scheme” was implemented also on the web to aid in describing how different types of combination products were currently defined by the OCP.

Three new RFDs were submitted to the OCP and five more combination products were assigned to Centers, all of which were drug-device combinations. Three of those assignments were holdovers from the first quarterly progress report. Again, all assignments were made within sixty days of receipt of the RFD from the manufacturer. Thus, after six months of operation, the OCP had completed nine combination product assignments to the three Centers, with one assignment remaining.³²⁴

³²³ See Second Quarterly Report, *supra* n.310.

³²⁴ *Id.*

Delving deeper into the statistics provided in the second quarterly report, the mean³²⁵ “total FDA review time,” or the time elapsed between receipt of the RFD from the manufacturer and the action letter generated by the OCP with the Center assignment for the product, was shortened by nearly a day. The median³²⁶ total review time, however, increased from 36.5 to 40 days. While this trend would not comfort the supporters of the OCP because it did not indicate a more timely and effective review process, the import of this statistic was lessened when viewed against the range of total FDA review times. In the first quarter, review times ranged between 29 and 46 days.³²⁷ In the second quarter, by contrast, review times ranged between 18 and 47 days.³²⁸ Thus, in the first quarter of 2003, half of the product assignment reviews were completed in 29 to 36.5 days and half were completed in 36.5 to 46 days. In the second quarter of 2003, once the OCP had assumed completely the reins of product assignment from the Office of the Ombudsman, half of the product assignments took between 18 and 40 days, and the other half of the assignments were made in 40 to 47 days. So the median shifted upwards from the first to the second quarter of 2003, but the mean review time changed a negligible amount, and the total review time for at least one product was shortened by eleven days. While the sample set of combination products used in these statistics was not extensive,³²⁹ the message conveyed by the statistics enhances the theme of the second quarterly progress report outlined above: the undeniable advantages in time and communication that accrued to both the FDA and combination product manufacturers as a result of the OCP’s consolidated oversight.

VI.C. The First Year Draws to a Close

³²⁵The “mean,” in statistics, is the average value of a set of numbers. AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE (4th ed. 2000).

³²⁶The “median,” in statistics, is the middle value in a distribution, above and below which lie an equal number of values. AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE (4th ed. 2000).

³²⁷See First Quarterly Report, *supra* n.310.

³²⁸See Second Quarterly Report, *supra* n.310.

³²⁹Recall that the OCP completed only four product assignments in the first quarter of 2003 and five product assignments in the second quarter. See *supra* n.310.

Although the OCP was officially created on December 24, 2002, the MDUFMA was enacted on October 26, 2002. Included within the MDUFMA was section 204(4)(G), that required the OCP to file a report with the appropriate Congressional committee “[n]ot later than one year after the date of the enactment of this paragraph and annually thereafter...”³³⁰ Also included within this statutory section were the three requirements that the OCP must satisfy within its report, namely a description of the (1) types of reviews undertaken by the OCP and their timely completion, (2) the consultations undertaken between Centers, and (3) the advances made in standardizing postmarket product regulation.³³¹ On October 26, 2003 the OCP presented its annual report to Congress to explain its progress through July 31, 2003.³³²

The annual report read much like an introductory primer to members of Congress and the general public who had not followed closely the creation and development of the OCP since late 2002. In fact, the report voiced the same preliminary concerns that were expressed at the beginning of the first quarterly progress report, produced at the end of March 2003.³³³ The broad responsibilities of the OCP, as well as its more specific regulatory goals, were reiterated as well. The report explained in more detail the OCP’s “performance” and its “additional activities and impacts” in each of the three statutorily specified areas.

VI.C.I. “Prompt Assignment of Combination Products”

³³⁰MDUFMA, section 204(4)(G), 21 U.S.C. § 353(g)(4)(G) (2004). *See also supra* n.272.

³³¹*Id.*

³³²Annual Report to Congress, at <http://www.fda.gov/oc/combination/congressreport.html> (last visited April 16, 2004). The entire report is twenty-three pages and therefore, an exhaustive examination of each finding by the OCP is beyond the confines of this paper. A summary of those findings, however, will still serve to illustrate the advances achieved by the OCP through July 31, 2003.

³³³*See supra* n.310.

By July 31, 2003, the OCP had received twelve RFDs for combination products and had assigned ten of those products to one of the three Centers; one request was withdrawn and the final request had not been assigned but was not behind schedule.³³⁴ The ten assignments that had been made were all made within sixty days of the OCP's receipt of each RFD, as mandated by 21 C.F.R. § 3.8. In a minimal departure from the statistics of the second quarterly progress report, the mean total review time increased again to 36.9 days, the median total review time decreased by one day to 39 days, and the range of review times increased again equal to the range originally cited in the first quarterly progress report, between 29 and 46 days. The minimal change in these statistics implied that the OCP may have settled into its expected rate of product assignment by the end of its seventh month.

Aside from the performance statistics used to illustrate the OCP's initial success in assigning Center jurisdiction, the report detailed additional steps by the OCP to act on its assignment role. Many of the findings were repetitive of what was cited in the first two quarterly progress reports, such as the responses to stakeholder inquiries and the establishment of the RFD database to serve as prior assignment precedent. Of especial note in the annual report, however, was the finding regarding the definition of the "primary mode of action." The OCP stated that a team comprised of employees from the OCP, each Center, and the Office of Chief Counsel (OCC) was still working on creating a clearer standard to be employed when the FDA made jurisdictional decisions.³³⁵ The result of that work was expected to change 21 C.F.R. part 3 (the applicable combination product regulations) to include that new standard. Assignment letters sent to product manufacturers were

³³⁴ See *supra* n.332.

³³⁵ *Id.*

modified to explain the full scope of regulatory requirements that each product would face. Finally, the OCP reinstated monthly meetings between its “jurisdictional and assignment specialists” and the separate Center product jurisdiction officers to discuss pending RFDs and enhance the uniformity of cross-Center decisions.³³⁶

VI.C.II. “Timely and Effective Premarket Review”

The performance statistics provided by the OCP to illustrate its “timely and effective” actions were more complex than those cited in its assignment decisions. First, the Centers had to adopt a system of designating applications as including a combination product; that adoption became effective on April 1, 2003. In response, two of the Centers, CBER and CDER, made that designation at the time that the application was submitted. CDRH, by contrast, made that designation once the review decision about the product had been made.³³⁷ Thus, when the OCP reported that 49 applications between April 1, 2003 and July 31, 2003 were classified as combination products, 38 of those applications were *received* by CBER and CDER and the remaining eleven applications that came from CDRH were actually applications with final decisions attached to them. The OCP further noted that too little time had passed between the adoption of this classification scheme and the preparation of the annual report to draw any meaningful conclusion about the timeliness and effectiveness of the Centers’ review procedures for NDAs, BLAs, or PMAs involving combination products.³³⁸ The OCP did note that between May 1, 2003 and July 31, 2003, however, all of the final decisions that CDRH issued with respect to four combination product 510(k) applications were reviewed within their statutory timeframes.³³⁹

³³⁶ *Id.*

³³⁷ *Id.*

³³⁸ *Id.* For information on NDAs, *see supra* n.28. For information on PMAs, *see supra* n.50. For information on BLAs, *see supra* n.69.

³³⁹ *Id.* For information on 510(k) applications, *see supra* n.51.

One other statistic compiled by the OCP for the report tracked the number of inter-Center consultations that were solicited prior to July 31, 2003. CBER asked for 24 consultations (mostly with CDRH), CDER asked for 14 consultations (drawing heavily from CDRH too), and CDRH requested 43 consultations (forty of which were with CDER). The OCP noted that many applications actually required multiple consultations and that applications received prior to April 1, 2003 for which consultations were solicited were not reflected in these data. Not all inter-Center consultations may have been recorded during the initialization of this procedure immediately after April 1, 2003. Once the web-enabled database was completed, however, the OCP anticipated the automatic recording of these consultation requests.³⁴⁰

The extensive nature of the changes that were documented by the OCP in this area indicated that the OCP had devoted much of its energy during the first half of 2003 to completing more “timely and effective” product reviews.³⁴¹ Again, many of the cited changes reiterated what had been explained to stakeholders in the quarterly progress reports. Generally, the OCP worked strenuously to facilitate inter-Center communication, from the implementation of an inter-Center mail courier system, to repeated training sessions on inter-Center consultations, to active monitoring of those consultations and of multidisciplinary review teams employing the revised Standard Operating Procedures,³⁴² to modernized internal electronic databases. An internal working group was charged with simplifying submission procedures, while another group was aided by OCP

³⁴⁰*Id.*

³⁴¹For an update of the OCP’s rate of product assignment between October 1, 2003 and March 31, 2004, see FY04 OCP Review Performance: Formal Requests for Designation Submitted by Industry, at <http://www.fda.gov/oc/combinatoin/fy04rfd.html> (last visited September 6, 2004). In that period, the OCP made 12 combination product assignments, mostly to CDRH, and spent between 20 and 58 days reviewing those requests for designation.

³⁴²*See supra* n.241.

in establishing specific review processes for “complex regulatory issues.”³⁴³ Finally, a retrospective review of these consultations and an analysis of the feedback solicited from Center employees involved in those product consultations informed the OCP as to how to coordinate future inter-Center communications.

VI.C.III. “Consistent and Appropriate Postmarket Regulation”

The third and final area that the OCP was assigned by statute to manage was the consistent oversight of combination product postmarket regulation. Although the OCP did not effect as much change in this area as it did in the premarket review arena, new postmarket reporting requirements for combination products were conceived by drawing from other regulatory sources.³⁴⁴ In essence, the OCP’s actions indicated that a more uniform and more tailored postmarket regulation of combination products could occur only if product manufacturers were informed properly at every step of the regulatory cycle. As mentioned *supra*, the OCP modified the assignment letters initially sent to manufacturers to be more explicit about the regulatory requirements that a manufacturer could expect. Then, at the end of the regulatory review process, the OCP saw a further chance to explain its expectations. Not only would the OCP actively support the Centers in their specific postmarket regulatory requirements, but it had already formed a working group to update policy and guidance statements on good manufacturing practices, quality system regulations, adverse event reports, and registration and listing mechanisms for approved combination products.³⁴⁵

VI.D. Moving Forward

³⁴³ See *supra* n.332.

³⁴⁴ *Id.* Statistical analysis was not presented by the OCP in this area.

³⁴⁵ *Id.*

The regulation of combination products, while requiring a clear framework based upon common product classifications and accepted administrative channels, must be flexible enough to manage the ever increasing sophistication of new products. To that end, the OCP has proposed at least two changes in its own oversight procedures. It has drafted a guidance to manage timeliness disputes, when the lead Center has not reviewed and acted on the manufacturer's product submission in an appropriate time frame.³⁴⁶ The guidance would help to define when the dispute should be presented to the OCP for resolution. On another oversight front, the OCP issued a proposed rule on May 7, 2004 to codify the definition of "primary mode of action"³⁴⁷ and to expedite the process of assigning product regulation to one Center by giving a manufacturer an "assignment algorithm" to use when requesting a product classification pursuant to the newly defined primary mode of action.³⁴⁸ Providing a definition for "primary mode of action," the OCP believes, would clarify the regulatory process. In addition, while the new definition would further the OCP's current practice of assigning jurisdiction based upon the primary mode of action, it would enhance that practice by providing a regulatory route when the primary mode of action can not be clearly determined.³⁴⁹

The OCP then allowed the comment period on its definition to extend through August 20, 2004, to permit product manufacturers and other interested parties to offer their alternative definitions or suggestions.³⁵⁰

The primary mode of action would be "the single mode of action of a combination product that provides the most important therapeutic action of the combination product."³⁵¹ If the most important therapeutic³⁵²

³⁴⁶ See Draft Guidance for Industry: Combination Products Timeliness of Premarket Reviews Dispute Resolution Guidance, <http://www.fda.gov/oc/combination/dispute.html> (last visited September 6, 2004).

³⁴⁷ See *supra* n.108.

³⁴⁸ FDA Proposes Rule on Combination Products, at <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01288.html> (last visited September 6, 2004); see <http://www.fda.gov/oc/combination/pmoaslides/sld001.html> (last visited September 6, 2004). See also 69 Fed. Reg. 25527 (May 7, 2004).

³⁴⁹ See <http://www.fda.gov/oc/combination/pmoaslides/sld007.html> (last visited September 6, 2004).

³⁵⁰ See 69 Fed. Reg. 35277 (June 24, 2004).

³⁵¹ See <http://www.fda.gov/oc/combination/pmoaslides/sld004.html> (last visited September 6, 2004).

³⁵² The OCP would define "mode of action" as "the means by which a product achieves a therapeutic effect." The term "therapeutic" would include "any effect of action of the combination product intended to diagnose, cure, mitigate, treat, or

action could not be determined, then the proposed assignment algorithm would be applied. Any assignment of Center jurisdiction would seek first to maintain regulatory consistency.³⁵³ In other words, a new combination product should be assigned to the Center that has experience in managing other products that raise the same questions of safety and effectiveness. If institutional consistency could not be preserved, perhaps because there are no similar older products, then the algorithm would dictate that the Center with the most related experience to the safety and effectiveness issues of the new product would receive jurisdiction.³⁵⁴ Such a definition and its accompanying algorithm, if adopted by the OCP at all, would be effective after the date of any final rule based upon this proposal. At this time, the OCP's final decision as to this definition and algorithm is pending, but the result will inevitably encompass the input of both private and public sector entities.

VII. Conclusion

The first annual report to Congress, now nine months old, in reality captured just the first seven months of the OCP's existence. Yet, it represented the culmination of decades of work on the part of the FDA to regulate the forefront of medical technology. Such a broad delegation of authority as the OCP received from the MDUFMA, to restore the cooperation between Centers confronted by divergent considerations while charting new administrative territory over combination products that defy traditional classifications, could have overwhelmed the infant Office before it could effect even one significant change. But the OCP drew on

prevent disease, or affect the structure or any function of the body." Combination products would be expected to have more than one mode of action. See <http://www.fda.gov/oc/combo/pmoasides/sld002.html> (last visited September 6, 2004).

³⁵³ See <http://www.fda.gov/oc/combo/pmoasides/sld005.html> (last visited September 6, 2004).

³⁵⁴ See <http://www.fda.gov/oc/combo/pmoasides/sld006.html> (last visited September 6, 2004).

its greatest strength to bear that authority: the expertise and the cooperation of the staff already employed by its sister Centers. Perhaps in one regard, then, the OCP was given a simpler task than it first appeared. The dedication to regulatory integrity and procedural fairness was already present in the reviewers and the jurisdiction officers. The OCP had just to bring these people together and to initiate a dialogue among them, whether through inter-Center review teams, or internal electronic databases, or employee training sessions.

To examine this relationship one step further, however, is to discover that such a reunion of experience is not simple. Decades of ad hoc decision making by the Centers, although tempered by the Intercenter Agreements of 1991, had created three unique pathways of approval that caused confusion among the Centers and consumed the temporal and financial resources of product manufacturers. The OCP had to interface different regulatory methods for markedly different products from the point of application to the point of product approval. Electronic resources had to be created. Consultation and collaboration had to be initiated and nurtured consistently. What the annual report provided was proof that such a reunion could occur, and in fact it *had* occurred.

Several observations about the future of the OCP could be made with relative certainty. The OCP will probably continue its web-enabled march to facilitate communication among the Centers, as the wireless Internet and other electronic advances make paper and telephones obsolete. New products will challenge the strength of that intercommunication routinely, as the forefront of science (especially with respect to drug-device combinations) pushes into unexplored and unimagined territory. A new generation of FDA staff will be raised on such intercommunication without sacrificing its sense of responsibility toward the health of

the American public. Although the MDUFMA provides sunset provisions for the OCP, beginning in 2007, it is acknowledged currently that the OCP will become so integral to the efficient and effective operation of the Centers that its dissolution will not, and in truth could not, occur. Thus, Congress should be content with the knowledge that, while the OCP would have been an appropriate addition to the FDA even in 1990, its creation in 2002 came not a moment too soon.