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## Can Regulation be as Innovative as Science and Technology? The FDA's Regulation of Combination Products

Susan Bartlett Foote\* & Robert J. Berlin\*\*

### INTRODUCTION

The twentieth century witnessed significant and continuous advances in medical product innovation, with breakthroughs in pharmaceutical, engineering and bioscience fields that revolutionized health care services. However, with innovation comes potential risk. Congress has been concerned about risks associated with medical products since the early 1900s,<sup>1</sup> and has, over time, empowered the U.S. Food and Drug Administration (FDA) to ensure that new medical products meet evolving standards of safety and effectiveness. The Food, Drug, and Cosmetic Act (FDCA) has been amended numerous times since the early 1900s, often in reaction to both perceived and real risks associated with new medical products.<sup>2</sup> The result is a complex regulatory apparatus that administers a variety of legislative mandates specifically tailored to the unique features of drugs, medical devices and biologics.

In recent years, scientific and technological advances in the fields of tissue engineering, cell biology, gene therapy and materials science, to name a few, promise breakthroughs that

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1. See Biologics Act of 1902, ch. 1378, 32 Stat. 728 (1902) (codified as amended at 42 U.S.C. § 262 (2000)). Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768, 768-70 (1906) (repealed 1938).

2. *E.g.*, Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16, 104 Stat. 4511, 4526 (1990) (current version at 21 U.S.C. § 353(g) (2000)); Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (current version at 21 U.S.C. § 301 (2000)); Medical Device Amendments of 1976, Pub L. No. 94-295, 90 Stat. 539, 540-42 (1976) (current version at 21 U.S.C. §§ 360c-360k (2000)).

no longer fit the clear statutory distinctions among drugs, medical devices, or biologics. These products, known as “combinations” because they mix attributes of drugs, biologics, or medical devices, challenge the FDA to adapt its regulatory schema to these novel combinations.<sup>3</sup>

The purpose of this article is threefold. First, we provide an overview of the innovation pipeline of combination products to illustrate the depth and breadth of the potential contributions of this field. Second, we summarize the evolution of the FDA over the last one hundred years and evaluate its initial efforts since 1990 to accommodate combination products. We find that the combination product provisions in statute and regulation follow a sequence that includes: a focus on definitions to distinguish between types of products as they emerge, a willingness by the FDA to stretch the limits of the definitions as new products evolve, and congressional intervention, often in reaction to crises or external pressures, to revise old definitions to reflect changes in product types. Third, we discuss why the traditional response to innovation may be ill-suited to the accelerated pace of the combination product revolution. We evaluate the likely responses of Congress, the FDA, and the regulated entities to possible changes in the approach to combination product regulation. We hope that our analysis will add to the understanding of the current regulatory environment and inform the on-going policy debate.

## I. OVERVIEW OF SCIENCE AND TECHNOLOGY OF COMBINATION PRODUCTS

We are now in an era of tremendous innovation in medical products that promises to transform medicine as we know it. This era is also characterized by new forms of innovation. In the twentieth century, there were major advancements in the fields of pharmaceuticals, engineered devices, and biologics. A new generation of products, however, combines attributes of these three formerly distinct fields. While it is impossible to predict with accuracy the next generation of medical product advances, it is clear that many will take the form of combination products.

The earliest combinations involved adding a

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3. See, e.g., Definition of Primary Mode of Action of a Combination Product, 69 Fed. Reg. 25,527, 25,528-30 (proposed May 7, 2004) (to be codified at 21 C.F.R. pt. 3).

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pharmaceutical agent to a therapeutic device, such as putting a steroid drug on a pacemaker electrode to speed healing and reduce scarring.<sup>4</sup> The recently introduced drug-eluting stents fall into this drug-device combination category.<sup>5</sup>

Tissue engineering and tissue replacement is a burgeoning area of growth that involves various combinations of biologics, devices, and drugs. Scientists have found that matrix scaffolds can serve as a mechanical substrate for regeneration of cartilage.<sup>6</sup> Adding components, such as growth factors, cells, or nutrients, hasten the growth of new tissue. There are many applications and potential uses for tissue engineered products, including tissue substitutes for burns, ulcers and reconstruction to the development of structural tissue products, organs, and organ systems.<sup>7</sup>

Another growth area for combination product research is in the field of gene therapy. Cells must be targeted for the delivery of modified gene sequences. Delivery mechanisms may include viruses (a biologic)<sup>8</sup> or synthetics, such as natural or synthetic lipids or purely synthetic polymers (a device).<sup>9</sup> Other drug delivery mechanisms may be device-like in nature, such as leads to thread through the venous system to targeted organs or sites within the body.

Nanomedicine is the monitoring, repair, construction and,

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4. See John Carey, *Combo Medicine*, BUSINESSWEEK, Mar. 25, 2003, available at <http://www.KeepMedia.com/pubs/businessweek/2003/03/25/18043>.

5. See *id.*

6. Lichun Lu, et al., *Biodegradable Polymer Scaffolds for Cartilage Tissue Engineering*, CLINICAL ORTHOPEDICS & RELATED RES, Oct. 2001, at S251-252, available at <http://gateway.ut.ovid.com/gw2/ovidweb.cgi>.

7. See Amy J. LaForte, *Bone Morphogenetic Protein Combination Products and Orthopedic Repair*, in NAT'L RESEARCH COUNCIL, PROCEEDINGS FROM THE WORKSHOP ON SCIENCE-BASED ASSESSMENT: ACCELERATING PRODUCT DEVELOPMENT OF COMBINATION MEDICAL DEVICES 15 (Bonnie A. Scarborough ed., 2004) [hereinafter NAT'L RESEARCH COUNCIL]; William McKay, *Product Development Process for a Bone Morphogenetic Protein Combination Product*, in NAT'L RESEARCH COUNCIL, *supra*, at 15; Robert S. Schwartz, *Drug-Eluting Stents*, in NAT'L RESEARCH COUNCIL, *supra*, at 18; H. Semih Oktay, *Drug-Eluting Stents: Preclinical Testing Challenges*, in NAT'L RESEARCH COUNCIL, *supra*, at 19; Ronald A. Sahatjian, *Taxus: A Polymer-Based Paclitaxel-Eluting Stent*, in NAT'L RESEARCH COUNCIL, *supra*, at 20.

8. Lonnie D. Shea & Tiffany L. Houchin, *Modular Design of Non-viral Vectors with Bioactive Components*, 22 TRENDS IN BIOTECHNOLOGY 429, 429 (2004).

9. Tristan Montier et al., *Non-viral Vectors in Cystic Fibrosis Gene Therapy: Progress and Challenges*, 22 TRENDS IN BIOTECHNOLOGY 586, 587 (2004).

control of human biological systems at the molecular level, using engineered nanodevices and nanostructures. Promising novel combinations in the nanotechnology pipeline include nanorobots that can travel through the body to find illness and target the delivery of drugs and biologics.<sup>10</sup> Microelectromechanical systems (MEMS) devices are tiny mechanical and electrical elements integrated onto a silicon chip to perform functions such as sensing. These compact devices with sophisticated functionality have many potential biomedical uses, including precision drug delivery using integrated microvalves and pumps, and portable biochemical analysis instrumentation using microfluidic networks.<sup>11</sup>

Some of these innovations have already come to the market, but many of them are in the research and development phase. The FDA has reviewed several hundred combination-type products since the term was statutorily defined; data now compiled by the agency shows that there were approximately sixty-one requests for designation (RFD) as combination products between October 1, 2003 and September 30, 2004.<sup>12</sup>

The innovative scientists and engineers in these and related fields face many challenges in the development of these products. But they will all have to navigate through the FDA process. Can regulation be as innovative as science and technology?

## II. HISTORY OF REGULATORY EVOLUTION

The over one hundred years of U.S. regulation of medical products provides a rich narrative history reflecting a cycle of scientific innovation and regulatory response. There are numerous extensive analyses of this history, which we commend to the interested reader.<sup>13</sup> The purpose of our

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10. See John Miller, *Beyond Biotechnology: FDA Regulation of Nanomedicine*, 4 COLUM. SCI. & TECH. L. REV. 1-2 (2003).

11. See Yvonne Carls-Powell, *Developing MEMS for Medicine*, 200 OE REPORTS, Aug. 2000, at <http://www.spie.org/web/oer/august/aug00/stanford.html> (last visited Nov. 7, 2004).

12. OFFICE OF COMBINATION PRODS., U.S. FOOD AND DRUG ADMIN., FY04 OCP REVIEW PERFORMANCE, at <http://www.fda.gov/oc/combo/fy04rfd.html> (last visited Nov. 7, 2004). Thirty-four of the sixty-one products for which designation was requested were categorized as combination products between October 2003 and September 2004. *Id.*

13. See generally SUSAN BARTLETT FOOTE, MANAGING THE MEDICAL

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cursory overview is to describe how policy adapted to new products. When a new type of product is considered as a target for regulation, there has often been a focus on classification of the product type through detailed definitions. “Definitional controversies are an established feature of food and drug law, driven by the differential treatment of the various categories of FDA-regulated products.”<sup>14</sup> The agency has tended to try to stretch its authority to clarify gray areas as new product types emerge. There often has been a congressional reaction, triggered by external crises or pressure, to revisit the definitions and amend FDA authority. The result is a patchwork of legislative mandates and a silo effect, with differently defined products being regulated differently. The following discussion elucidates this pattern for the three medical product categories—drugs, medical devices, and biologics.<sup>15</sup>

## A. EARLY DRUG AND DEVICE REGULATION

Public concern about fraud in the sale of food and medicine grew during the 1880s and 1890s in response to diseased or adulterated foodstuffs. Because there were few effective drugs at this time, and most were not purchased directly through medical doctors, drugs were seen as part of food regulation. Many nostrums and medicines contained dangerous habit-forming narcotics.<sup>16</sup> Harvey W. Wiley, Chief of the Division of Chemistry at the Department of Agriculture, became a

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ARMS RACE: INNOVATION AND PUBLIC POLICY IN THE MEDICAL DEVICE INDUSTRY (Univ. of Cal. Press, 1992); PETER BARTON HUTT & RICHARD A. MERRILL, *FOOD AND DRUG LAW: CASES AND MATERIALS* (2d. ed. 1991); CHARLES O. JACKSON, *FOOD AND DRUG LEGISLATION IN THE NEW DEAL* (1970); Susan Bartlett Foote, *Loops and Loopholes: Hazardous Device Regulation Under the 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act*, 7 *ECOLOGY L.Q.* 101 (1978); Henry G. Grabowski & John M. Verson, *Consumer Protection Regulation in Ethical Drugs*, 67 *AM. ECON. REV.* 359 (1977); Peter Barton Hutt, *A History of Government Regulation of Adulteration and Misbranding of Medical Devices*, 44 *FOOD DRUG COSM. L.J.* 99 (1989); Vincent A. Kleinfeld, *Legislative History of the Federal Food, Drug, and Cosmetic Act*, 1 *FOOD DRUG COSM. L.Q.* 532 (1946); Symposium, *The New Food, Drug, and Cosmetic Legislation*, 6 *LAW & CONTEMP. PROBS.* 1 (1939).

14. Linda R. Horton, *Over-the-Counter Drug Authority Issues: Selected Topics*, 48 *FOOD & DRUG L.J.* 545, 551 (1993).

15. While the FDA also has regulatory power over foods, we restrict this analysis to drugs, biologics and devices.

16. Oscar E. Anderson, *Pioneer Statute: The Pure Food and Drugs Act of 1906*, 13 *J. PUB. L.* 189, 189 (1964).

missionary for reform.<sup>17</sup> The publication of Upton Sinclair's *The Jungle* in 1905, with its graphic images of adulterated food, aroused the public to demand reform.

After years of unsuccessful efforts, the first major federal initiative was the Pure Food and Drugs Act of 1906.<sup>18</sup> The law defined drugs as separate from food, and extended the definition to include not only medicines recognized by the United States Pharmacopoeia (USP), but also any substance intended for the cure, mitigation, or treatment of disease, bringing proprietary medicines within the scope of the law.<sup>19</sup> The law conferred limited authority, allowing the federal government the authority to seize adulterated or misbranded articles on the market. The Department of Agriculture, Division of Chemistry, was charged with enforcing the new law.

Enforcement activities against adulterated foods and drugs increased throughout the 1920s. By 1931, the FDA had been established within the Department of Agriculture. Officials were severely handicapped in reaching the adulterated products because of the limitations of the seizure authority.<sup>20</sup> The new Roosevelt Administration supported expanding federal authority in 1933, although it took over five years of effort to enact reforms.<sup>21</sup>

In the debates leading up to the subsequent legislation, there was reference, for the first time, to medical devices. An FDA report in 1933 stated:

Mechanical devices, represented as helpful in the cure of disease, may be harmful. Many of them serve a useful and definite purpose. The weak and ailing furnish a fertile field, however, for mechanical devices represented as potent in the treatment of many conditions for which there is no effective mechanical cure. The need for legal control

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17. OSCAR E. ANDERSON, *THE HEALTH OF A NATION: HARVEY W. WILEY AND THE FIGHT FOR PURE FOOD* 1-16 (University of Chicago Press, 1958).

18. Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768, 768-72 (1906) (repealed 1938).

19. Since 1820, the USP has set standards for medications used by the American public. It is an independent, nonprofit corporation composed of delegates with expertise in medicine. The 1906 law recognized the USP standards. Proprietary drugs are those sold directly to the public, and they include patent medicines. The term proprietary indicates that the ingredients are secret, not that they are patented. *See generally* USP Website, at <http://www.usp.org/> (last visited Apr. 22, 2005).

20. David F. Cavers, *The Food, Drug and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions*, 6 LAW & CONTEMP. PROBS. 2, 15-16 (1939).

21. *See id.* at 2, 3 n.9.

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of devices of this type is self-evident . . . . The new statute, if enacted, will bring such products under the jurisdiction of the law.<sup>22</sup>

There was heated Congressional debate over how to define drugs and devices. An early Senate bill would have defined drugs to include all substances, preparations and devices “intended for use in the cure, mitigation, treatment or prevention of disease.”<sup>23</sup> When this language was debated in the Senate, there was no objection to regulation of devices, but instead controversy about defining them as drugs. One Senator argued that to treat devices as drugs “in law and in logic and in lexicography is a palpable absurdity.”<sup>24</sup>

The bill addressing concerns about drug and device authority languished in Congress until a drug disaster focused public attention. The Massengill Company produced a liquid form of sulfanilamide, one of the new classes of sulfa drugs on the market. The solution was toxic and one hundred people died after ingesting the elixir.<sup>25</sup>

The resulting legislation responded to the public pressure for reform, and set drugs and devices on different pathways from a regulatory perspective. The 1938 law specifically defined “new drugs” as distinct from drugs, and expanded the FDA’s power over them.<sup>26</sup> For the first time, the agency could subject “new drugs” to pre-market controls, rather than just the authority to seize misbranded or adulterated products.<sup>27</sup> The legislation also defined medical devices for the first time.<sup>28</sup> However, by definition they were not “new drugs” so the pre-market authority did not apply.<sup>29</sup> Medical devices were now

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22. U.S. DEP’T OF AGRIC., REPORT OF THE CHIEF OF THE FOOD AND DRUG ADMINISTRATION, 13-14 (1933).

23. S. REP. NO. 493, at 2 (1934).

24. Bruce C. Davidson, *Preventive “Medicine” for Medical Devices: Is Further Regulation Required?*, 55 MARQ. L. REV. 405, 415 (1972) (quoting Senator Clark).

25. See Foote, *Loops and Loopholes*, *supra* note 13, at 106.

26. See Cavers, *supra* note 20, at 32-33, 40.

27. See *id.*

28. See *id.*

29. The definitions are as follows:

The term “drug” means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in



subject to regulation, but only to the provisions referring to adulteration and misbranding of products already on the market.<sup>30</sup>

The pattern of careful definition of products by category and tailoring regulatory authority to these definitional distinctions emerged. It was also clear that external pressure, often in the form of crises of some kind, helped to stir Congress into action.

Another tragedy spurred major new drug legislation in 1962. In the 1950s, thalidomide, a sedative, was approved in Europe.<sup>31</sup> Hundreds of pregnant women who took the drug gave birth to children with serious deformities.<sup>32</sup> Although the drug was only approved for limited distribution in the United States, news of the link between thalidomide and the deformed children in Europe facilitated the passage of amendments to the FDCA that were pending at the time.<sup>33</sup> Under the 1962 amendments, requirements for pre-market drug approvals increased to include a finding of efficacy as well as safety.<sup>34</sup> These amendments put additional distance between the drug and the device authorities.

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clause (A), (B), or (C).

21 U.S.C. § 321(g)(1)(2000).

The term "device" (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is -- (1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, (2) intended for the use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure of any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

*Id.* § 321(h) (2000).

30. See Cavers, *supra* note 20, at 31-37.

31. HARVEY TEFF & COLIN MUNRO, THALIDOMIDE: THE LEGAL AFTERMATH 1 (Saxon House, 1976).

32. *Id.* at 4-5.

33. *Id.* at 118-24.

34. *Id.* at 123.

## B. DEVICE REGULATION EXPANDS

Throughout the 1950s and 1960s, the medical device industry grew in size and the products grew in complexity. Examples include monitoring equipment in coronary care units, automated laboratory equipment, new implanted devices such as pacemakers, and a myriad of diagnostic and therapeutic instruments.<sup>35</sup> During this period, the Bureau of Drugs continued to enforce both the drug and device provisions.

Confronted with inadequate regulatory powers of the more complex medical devices, the FDA tried to stretch the limits of its authority by classifying some devices as drugs under the 1962 law. In 1968, the Second Circuit upheld the FDA's classification of a nylon ligature loop and nylon locking disk used to tie off severed blood vessels during surgery as a drug. In *AMP v. Gardner*,<sup>36</sup> the court broadly construed the definition of drug by emphasizing the public health goals of the law, holding that a medical product not generally recognized as safe and effective could be termed a "drug" and regulated as such.<sup>37</sup> In the next year, the Supreme Court also broadly construed the term "drug" to apply to an antibiotic disk in *United States v. An Article of Drug . . . Bacto-Unidisk. . .*<sup>38</sup> In *Bacto-Unidisk*, the Court concluded that the term "drug" was a legal term of art which could be "given a liberal construction consistent with the [FDCA's] overriding purpose to protect the public health."<sup>39</sup>

There was growing legislative interest in expanding medical device regulation during the 1960s as recognition of the problems grew. Court decisions had confused the situation for manufacturers who were uncertain about how their products would be regulated.<sup>40</sup> Bills to expand device regulation had been introduced during both the Johnson and Nixon Administrations.<sup>41</sup> In 1969, the Department of Health, Education, and Welfare (HEW), of which the FDA was a part, convened a study group to investigate the need for additional legislation. Named the Cooper Committee, after Chairman Dr.

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35. Theodore Cooper, *Device Legislation*, 26 FOOD DRUG COSM. L.J. 165, 166 (1971).

36. 389 F.2d 825 (2d Cir. 1968).

37. *Id.* at 829-31.

38. 394 U.S. 784 (1969).

39. *Id.* at 798.

40. Vincent A. Kleinfeld, *Sterile Disposable and Other Therapeutic Devices and the Law*, 27 FOOD DRUG COSM. L.J. 19, 21 (1972).

41. See Cooper, *supra* note 35, at 169.

Theodore Cooper, the group advocated new legislation, including a system to classify devices based on risk.

Seven years elapsed between the report of the Cooper Committee and the passage of the Medical Device Amendments (MDA) in 1976. During that time, numerous bills were proposed and debated. The controversies over intrauterine devices (IUDs) and extensive pacemaker recalls in the mid-seventies<sup>42</sup> stimulated public concern and legislative interest, much as the Elixir-Sulfanilamide disasters in 1938 and the thalidomide tragedy in 1962.<sup>43</sup> The FDA began to position itself for potential legislation. In 1971, the Office of Medical Devices was transferred from the Bureau of Drugs to the Office of the Associate Commissioner for Medical Affairs.<sup>44</sup> Three years later, in 1974, responsibility for regulating devices was vested in a new Bureau of Medical Devices and Diagnostic Products, later renamed the Bureau of Medical Devices (BMD).<sup>45</sup>

The MDA stepped up the regulatory authority over devices by providing “reasonable assurance of safety and effectiveness” for all devices.<sup>46</sup> Devices on the market the day the law passed included pre-1976 devices and devices later introduced which are similar or substantially equivalent to them, often called 510(k)s after the section of the legislation which regulates them. The new law distinguished between pre-1976 devices and devices first developed after the date the law passed. Congress described a classification scheme based on risk because of the variety of devices, ranging from simple tongue depressors to implantable cardiac pacemakers. Class I devices consist of those generally considered to present no risks, Class II devices are those whose characteristics are well known so

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42. See DEP'T OF HEALTH, EDUC., AND WELFARE, FOOD AND DRUG ADMINISTRATION'S INVESTIGATION OF DEFECTIVE CARDIAC PACEMAKERS RECALLED BY THE GENERAL ELECTRIC COMPANY 21 (1975); see generally *Regulation of Medical Devices (Intrauterine Contraceptive Devices): Hearings Before the Subcomm. on Intergovernmental Relations of the House Committee on Government Operations*, 93rd Cong. (1973).

43. Foote, *Loops and Loopholes*, *supra* note 13, at 110-11.

44. Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1803-04, n.157 (1996) (citing Peter Barton Hutt, *A History of Government Regulation of Adulteration & Misbranding of Medical Devices*, 44 Food Drug. Cosm. L.J. 99, 110-11 (1989)).

45. *Id.* The current name of the device authority is the Center for Devices & Radiological Health (CDRH).

46. Medical Device Amendments of 1976, Pub L. No. 94-295, 90 Stat 539, 541 (1976) (current version at 21 U.S.C. §§ 360c-360k (2000)).

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that safety and efficacy can be guaranteed through performance standards, and Class III devices are those whose safety and effectiveness are sufficiently uncertain that they cannot be determined without additional testing. Only Class III devices must meet pre-market approval requirements equivalent to new drugs. The law created a variety of regulatory pathways for medical devices, depending on how they were classified, when they were marketed, and their “equivalence” to products on the market when the law was passed.

Some have argued that Congress had hoped that its revision of the device definitions would end the issue of whether a particular product was a drug or a device. However, there were no mechanisms to resolve disputes in close cases. “Accordingly, there was a tendency . . . for the FDA to rule that a particular product was a drug rather than a device,” particularly if there was a combination of a drug and a device. The FDA took the position that although devices, as a matter of law, may not have those mechanisms of actions, there is nothing in the drug definition that restricts it to articles employing those mechanisms of action.<sup>47</sup>

From 1906 until the 1980s, Congress periodically expanded the FDA’s regulatory authority. It did so through discrete legislation that focused on detailed definitions of new products, such as drugs, new drugs, devices, discrete classifications of devices, and so on. The regulatory requirements followed the definitional categories. When regulatory authority did not fit the risks as defined by the FDA, the agency tended to stretch the confines of the law to accommodate its regulatory preferences. During this period, regulatory silos emerged to implement these very different legislative regimes. The drug regulation was administered by the Center for Drug Evaluation and Research (CDER); the Center for Devices and Radiological Health (CDRH) managed devices.

### C. BIOLOGICS REGULATION

At this point in our narrative, it is important to turn attention to the evolution of the regulation of biologics.

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47. Rodney R. Munsey, *Trends and Events in FDA Regulation of Medical Devices Over the Last Fifty Years*, 50 *Food & Drug L.J.* 163, 169 n.30. (1995) (citing a letter from William Randolph, Acting Associate Commissioner for Regulatory Affairs to Luster J. Lifton in response to an inquiry regarding the regulatory status of a saline solution).

Biologics followed a parallel but separate track from drugs and devices. The Biologics Act passed in 1902 in response to tetanus-causing microbes' contamination of batches of smallpox vaccine and diphtheria antitoxin. Biologics were defined as "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of disease of man."<sup>48</sup> Chronologically, it was the first significant attempt to regulate medical technology, but its importance was obscured by the passage four years later of the Pure Food and Drugs Act of 1906.

The focus of early biologics regulation was to prevent contamination during the manufacturing process, which was appropriate to the era when biologics were crude mixtures or biological extracts.<sup>49</sup> The law required that a manufacturer obtain a license for its biologic product, properly label the product and submit to inspection of its facilities. The initial authority to regulate was at the Treasury Department. The regulatory power was transferred to the Hygienic Laboratory in 1903, which later became the National Institutes of Health.<sup>50</sup>

Biologics were clearly distinguished from categories of drugs, relatively simple molecules that are chemically synthesized or extracted from plant and other sources of very high level of purity. However, despite the fact that the regulatory scheme, the responsible authority, and the products themselves differed from drugs, there were gray areas between these two categories. The FDA assumed jurisdiction over insulin in 1941 and antibiotics in 1945, despite the fact that "[b]oth products, and insulin in particular, had more in common with biologics than they did with pharmacological preparations."<sup>51</sup>

The Biologics Act was revised in 1944 as part of the Public Health Service Act<sup>52</sup> which added mandatory product licensure and specified the criteria for issuing license approvals. Additional changes occurred in biologics regulation in response to what was known as the "Cutter incident," when a number of

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48. Biologics Act of 1902, ch. 1378, 32 Stat. 728, (1902) (current version at 42 U.S.C. § 262 (2000)).

49. Gary E. Gamerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 FOOD & DRUG L.J. 213, 216-20 (1994).

50. *Id.* at 218 n.26.

51. *Id.* at 219.

52. Public Health Service Act, ch. 373, § 351, 58 Stat. 682, 702 (1944) (current version at 42 U.S.C. § 262 (2000)).

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children contracted polio from a batch of polio vaccine produced by Cutter laboratories.<sup>53</sup> The crisis was attributed to lax regulation and pressure at NIH to get the vaccine on the market. One result was the creation of the NIH Division of Biological Standards (DBS), which Congress transferred to the FDA in 1972. This unit eventually became the Center for Biologics Evaluation and Regulation (CBER).

Like the tensions between drug and device regulation, there were gray areas in the definitional distinctions between drugs, devices, and biologics. In the 1970s and 1980s, there was significant innovation in biopharmaceuticals that dissolved the traditional scientific boundaries among biologics, drugs and devices. Examples include recombinant insulin, diagnostic monoclonal antibodies, and interferon.<sup>54</sup> As one commentator noted, “[d]istinguishing the jurisdictional status of many biologics from traditional drug and device products became difficult for both the FDA and industry because some products had characteristics which met multiple statutory and scientific definitions.”<sup>55</sup>

By 1980, the FDA had three silos for regulating medical products- drugs, devices, and biologics. There were gray areas at the margins. The carefully crafted definitions often did not fit some innovations or the agency has to stretch its authority to regulate products. Inter-center rivalry and cultural traditions influenced the agency’s assessments.<sup>56</sup> The perception was that CDER played a dominant role among the Centers and exercised greater influence over the decisions. If a medical device had drug characteristics, it could get delayed due to the request for drug expert consultations or subjected to additional, often unexpected regulatory hurdles.<sup>57</sup> The regulatory process required the manufacturers to navigate through a maze of definitional and substantive hurdles, with significant differences in requirements based on how the product was ultimately classified.

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53. HUTT & MERRILL, *supra* note 13, at 517-18.

54. Gamberman, *supra* note 49, at 221.

55. *Id.* at 221 n.53 (citing Assignment of Agency Component for Review of Premarket Applications, 56 Fed. Reg. 58,754 (codified at 21 C.F.R. pt. 3 (1991))).

56. Kshitij Mohan, *Combination Products: Incrementalism Won't Work*, MED. DEVICE AND DIAGNOSTIC INDUSTRY, May 2002, at 3, available at <http://www.devicelink.com/mddi/archive/02/05/017.html>.

57. *Id.* at 2.

Before turning our attention to the FDA's recent approaches to combination products, it is important to note that the major legislation on FDA issues in the last twenty years has not disrupted the three silos created through the evolutionary process described above. This is true despite major shifts in the political environment. The Safe Medical Devices Act of 1990<sup>58</sup> expanded the FDA's enforcement and reporting authority without changing the Center structure. The FDA Modernization Act, passed after significant attacks on the FDA's consumer protection mission by the Republican Congress in 1995 and 1996, streamlined regulatory processes without changing the presumptions about the FDA's authority.<sup>59</sup> Two user fee bills, one for drugs in 1992 (PDUFA), followed ten years later by one for devices (MDUFMA), increased the funds available for FDA approvals through assessments on regulated entities, also without changing the fundamental regulatory structure.<sup>60</sup>

At the agency level, this period included continued turf battles among the three medical products centers. There was a perception among many that the CDER's approach dominated and was treated as superior to the other centers. The 1993 Temple Commission, led by long-time FDA official Dr. Robert Temple, reported serious reservations about the Device Center's scientific capabilities.<sup>61</sup> According to FDA expert Richard A Merrill, the message implicit in Commissioner Kessler's decision to authorize an inquiry into the device center processes was that they were not reliable and its personnel were not adequately trained.<sup>62</sup> In 2003, a shake up at CBER resulted in the transfer of jurisdiction over a number of

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58. Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16, 104 Stat. 4511, 4526 (1990) (current version at 21 U.S.C. § 353(g) (2000)).

59. See Larry Pilot & Daniel Waldmann, *Food and Drug Administration Modernization Act of 1997: Medical Device Provisions*, 53 FOOD & DRUG L.J. 267, 267, 272-74 (1998).

60. Prescription Drug User Fee Act of 1992 (PDUFA), Pub. L. No. 102-571, 106 Stat. 4491 (1992); Medical Device User Fee and Modernization Act of 2002 (MDUFMA), Pub. L. No. 107-250, 116 Stat. 1588 (2002).

61. See U.S. FOOD AND DRUG ADMIN., FINAL REPORT OF THE COMMITTEE FOR CLINICAL REVIEW: BASED ON A REVIEW OF SELECTED MEDICAL DEVICE APPLICATIONS, reprinted in SUBCOMM. ON OVERSIGHT AND INVESTIGATIONS OF THE HOUSE COMM. ON ENERGY AND COMMERCE, LESS THAN THE SUM OF ITS PARTS: REFORMS NEEDED IN THE ORGANIZATION, MANAGEMENT, AND RESOURCES OF THE FOOD AND DRUG ADMINISTRATION'S CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, 103rd Cong., (Comm. Print 1993).

62. Merrill, *supra* note 44, at 1826.

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biological products from CBER to CDER.<sup>63</sup> During this period of political change, and challenges to the FDA from the left and the right, the three separate Centers have survived.

### III. EVOLUTION OF COMBINATION PRODUCTS REGULATION

The development of combination products regulation follows the same iterative and incremental pathway that we have seen in the areas of drugs, devices, and biologics.

#### A. SAFE MEDICAL DEVICES ACT INTRODUCES COMBINATION PRODUCTS

The opportunity to obtain legislative guidance came in 1990 as part of the Safe Medical Devices Act (SMDA). During the 1980s, following the passage of the complex MDA in 1976, there was significant concern about the FDA's implementation of the law, the challenges built into the law itself, and limitations on FDA authority in some areas. The General Accounting Office (GAO) conducted a series of studies on FDA performance.<sup>64</sup> In response, the FDA initiated a multi-phase Action Plan to improve its timeliness, effectiveness, and efficiency in drug review, and to improve its medical device program.<sup>65</sup> Nevertheless, the drumbeat for legislation continued. The House Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce issued a report finding significant failures at the FDA to implement the law.<sup>66</sup> The Department of Health and Human

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63. See U.S. FOOD AND DRUG ADMIN. CTR. FOR BIOLOGICS EVALUATION AND RESEARCH, DEP'T OF HEALTH & HUMAN SERV., TRANSFER OF THERAPEUTIC PRODUCTS TO THE CENTER FOR DRUG EVALUATION AND RESEARCH, at <http://www.fda.gov/cber/transfer/transfer.htm> (updated Sept. 27, 2004). The report lists the products types to be transferred along with the staff comprising CBER's Office of Therapeutics Research and Review which transferred as well. *Id.* CDER created two new offices to accommodate the former CBER staff. *See id.*

64. See U.S. GEN. ACCOUNTING OFFICE, REPORT TO THE CONG., FED. REGULATION OF MEDICAL DEVICES -- PROBLEMS STILL TO BE OVERCOME (GAO/HRD-83-53, 1983); U.S. GEN. ACCOUNTING OFFICE, REPORT TO THE CHAIRMAN, COMM. ON GOVERNMENTAL AFFAIRS U.S. SENATE, MEDICAL DEVICES: EARLY WARNING OF PROBLEMS IS HAMPERED BY SEVERE UNDERREPORTING (GAO/PEMD-87-1, 1986).

65. U.S. FOOD AND DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERV., A PLAN FOR ACTION: PHASE II, at v-vi (1987).

66. HOUSE SUBCOMM. ON OVERSIGHT AND INVESTIGATIONS OF THE COMM. ON ENERGY AND COMMERCE, 98th Cong., MEDICAL DEVICE REGULATION: THE



Services (DHHS) developed a draft bill to make the device provisions more effective in 1985, and House Democrat Henry Waxman introduced H.R. 5516, Medical Device Improvements Act, in 1986.<sup>67</sup> Waxman also co-sponsored H.R. 2595, Medical Device Improvements Act, with Energy and Commerce Chair John Dingell, on June 3, 1987.<sup>68</sup> That bill died in the Senate in 1988, and the Safe Medical Devices Act (SMDA) was introduced on August 2, 1989.<sup>69</sup>

Combination product issues were not the primary concern of the House supporters and no provision related to combinations appeared in the House Report. However, industry representatives were able to persuade the Senate supporters that combination product reviews were a problem that needed to be addressed.<sup>70</sup> The Senate Report accompanying the bill noted the importance of combination products, including “devices impregnated with biologically-active materials, medicated devices, implantable drug pumps and biological sensors, and therapeutic devices used in conjunction with drugs for the extra-corporeal treatment of diseases.”<sup>71</sup> According to the report language, Sections 19 and 20 in the Senate bill established “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 of the combination product.”<sup>72</sup> The Senate bill also altered the definitions of “drug” and “device” to accommodate the principles of allocation of combination products through primary mode of

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FDA’S NEGLECTED CHILD 1-5 (Comm. Print 1983).

67. See Letter from Margaret M. Heckler, Secretary of Health and Human Services, to the Honorable Thomas P. O’Neill, Speaker of the House of Representatives (Apr. 17, 1985) (on file with author); H.R. 5516, 99th Cong. (1986).

68. H.R. 2595, 100th Cong. (1987).

69. After recounting the shortcomings of the FDA, the Honorable Henry A. Waxman stated “Mr. Speaker, I must note that we should not even be in the position of introducing further legislation with respect to the regulation of medical devices. Throughout the last Congress, we worked closely with representatives of the medical device industry to fashion a compromise bill.” 135 CONG. REC. E 2815 (1989) (statement of Rep. Henry A. Waxman) (introducing H.R. 3095).

70. “Various persons from industry have expressed the view that a weakness in FDA’s premarket review process is the determination of how to regulate combination products.” S. REP. NO. 101-513, at 43 (1990).

71. *Id.*

72. *Id.*; see also Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16, 104 Stat. 4526 (1990) (current version at 21 U.S.C. § 353(g) (2000)).

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action review. The SMDA became law in 1990.<sup>73</sup>

On November 21, 1991, the FDA published its final regulation on combination products pursuant to the SMDA.<sup>74</sup> The agency also developed inter-center agreements in order to clarify how the respective centers were to operate in allocating products based on an assessment of their primary mode of

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73. Section 19 amended the drug definition by deleting the words “but does not include devices or their components, parts, or accessories.” See S. REP. NO. 101-513, at 43. By deleting this language, a product whose primary mode of action is attributable to a drug, but has a device component, may be reviewed under the Act’s drug authority. *Id.* In addition, the word “primary” in the device definition was substituted for the word “principal” to conform to the new concept of primary mode of action. *Id.* The new legislative language reads:

(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.

S. REP. NO. 101-959, at 17 (1990).

74. Definition of a Combination Product:

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 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; (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 investigation drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

21 C.F.R. § 3.2(e) (2004).

action.<sup>75</sup>

The allocation process follows the iterative path we have described in our discussion of the evolution of drug, device and biologics previously. In this case, Senate bill recognized the difficulty of determining the jurisdictional base for regulating combination products.<sup>76</sup> It focused on defining terms and the allocation process.<sup>77</sup> The final bill did not disrupt the three silos that the Centers represent. Instead, the role of the allocation process is to establish “firm ground rules” to place a combination product into one of the three silos.<sup>78</sup>

Despite the legislative success in the SMDA, innovators in the field of combination products continued to experience challenges at the FDA.<sup>79</sup> The FDA acknowledged stakeholder issues including:

concerns about the consistency, predictability, and transparency of the process used to assign an FDA Center with primary responsibility for review and regulation . . . , issues related to the management of the review process when two (or more ) FDA Centers have review responsibilities for a combination product; lack of clarity about the postmarket regulatory controls applicable to combination products; and lack of clarity regarding certain agency policies, such as when applications to more than one Center are needed.<sup>80</sup>

Agency efforts did not resolve these issues, leading to pressure to formalize the allocation process.<sup>81</sup> Legislative authority was sought legislative authority to accomplish the task.<sup>82</sup>

The vehicle for this effort was the medical device user fee legislation that Congress had been considering for years. In 2002, Congress passed the Medical Devices User Fee and

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75. See U.S. FOOD AND DRUG ADMIN., INTERCENTER AGREEMENT BETWEEN THE CENTER FOR DRUG EVALUATION AND RESEARCH AND THE CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (1991), at <http://www.fda.gov/oc/ombudsman/drug-dev.htm>.

76. S. REP. NO. 101-513, at 30 (1990).

77. *Id.*

78. *Id.* See Safe Medical Devices Act of 1990, Pub. L. No. 101-629, 104 Stat. 4511 (1990) (current version at 21 U.S.C. § 353(g) (2000)).

79. OFFICE OF COMBINATION PRODS., U.S. FOOD AND DRUG ADMIN., DEP'T OF HEALTH & HUMAN SERV., ANNUAL REPORT TO CONGRESS: FEDERAL FOOD, DRUG, AND COSMETIC ACT AS AMENDED BY THE MEDICAL DEVICE USER FEE AND MODERNIZATION ACT OF 2002, at 4-5 (2003).

80. *Id.*

81. See *id.*

82. See *id.*

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Modernization Act (MDUFMA) of 2002.<sup>83</sup> MDUFMA also amended section 503(g) of the FDCA.<sup>84</sup> A provision in the bill modified definitions to specifically direct assignment to an agency center pursuant to new procedures.<sup>85</sup> These included the establishment of a new Office of Combination Products (OCP) within the office of the Commissioner to ensure prompt assignment and effective review, resolve disputes, and report on the impact of the office including the numbers and types of combinations, review times and improvements in consistency.<sup>86</sup> With congressional directives in place, the challenge of combination products was once again in the hands of the FDA.<sup>87</sup>

## B. PRIMARY MODE OF ACTION

The key challenge was to operationalize SMDA's "primary mode of action" language. On May 7, 2004, the FDA issued a Proposed Rule, "Definition of Primary Mode of Action of a Combination Product."<sup>88</sup> The proposed rule is "intended to promote the public health by codifying the agency's criteria for the assignment of combination products in transparent, consistent, and predictable terms."<sup>89</sup> As of this writing, the proposed rule is still pending.<sup>90</sup> Although the rule is not final, the language of the proposal, as well as the comments from interested parties, provides insight into the goals of the agency, and into the views of many drug, device and biologics manufacturers on this issue.

The FDA notes that "primary mode of action" (PMOA) is not defined in the statute or regulations, and may be difficult to identify by either the FDA or the product sponsor at the time assignment is being considered.<sup>91</sup> Accordingly, without clear

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83. Medical Device User Fee and Modernization Act of 2002, Pub. L. No. 107-250, 116 Stat. 1588((2002).

84. *See id.*

85. *See id.*

86. *See* 21 U.S.C. §353(g) (2000).

87. Product Jurisdiction, 21 C.F.R. §§ 3.1-3.10 (2003).

88. Definition of Primary Mode of Action of a Combination Product, 69 Fed. Reg. 25,527 (proposed May 7, 2004) (to be codified at 21 C.F.R. pt. 3).

89. *Id.*

90. The original comment period was to close on July 6, 2004, but was extended to August 20, 2004. *See* Definition of Primary Mode of Action of a Combination Product, 69 Fed. Reg. 35,277 (June 24, 2004).

91. Definition of Primary Mode of Action of a Combination Product, 69 Fed. Reg. at 25,527.

definitions of “mode of action” and “primary mode of action,” the assignment process may “appear to be unpredictable.”<sup>92</sup> The rule also sets forth a two-tiered assignment algorithm to use to determine assignment in some circumstances.<sup>93</sup> The proposed rule defines “mode of action” as “the means by which a product achieves a therapeutic effect” and “primary mode of action” as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product.”<sup>94</sup> If the agency cannot determine the primary mode of action, the assignment algorithm would apply.<sup>95</sup> The next step asks: is there an agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination as a whole?<sup>96</sup> If not, the question becomes, “[w]hich agency component has the most expertise related to the most significant safety and effectiveness questions presented by the product?”<sup>97</sup>

Interested manufacturers, trade associations, and professional organizations submitted comments to the proposed rule.<sup>98</sup> While most of the comments welcomed the effort and offered specific responses, a consistent theme emerges. There is concern, expressed in different ways, that the FDA not deviate from the terms of the statute (both SMDA and MDFUMA), and respect prior assignment precedents.<sup>99</sup> For example, the National Electrical Manufacturers Association<sup>100</sup> states that:

the proposed rule, with its creation of an algorithm for determination of the appropriate Center to assign a combination product, would, if adopted, violate the intent of Congress expressed in MDUFMA by introducing two criteria for assignment of a combination product which were not included within the statute when it was enacted.<sup>100</sup>

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92. *Id.* at 25,528.

93. *Id.*

94. *Id.*

95. *Id.* at 25,529.

96. *Id.*

97. Definition of Primary Mode of Action of a Combination Product, 69 Fed. Reg. at 25,530.

98. There are twelve posted comments available on the FDA Dockets site. FOOD AND DRUG ADMIN., COMMENTS ON DEFINITION OF PRIMARY MODE OF ACTION OF A COMBINATION PRODUCT DOCKET 2004 N-0194, at <http://www.fda.gov/ohrms/dockets/FDARULE/2004npr.htm#august2004> (last visited Nov. 7, 2004).

99. *Id.*

100. Letter from Robert G. Britain, Vice President, Medical Products,

Smith and Nephew Wound Management expresses concern about agency discretion: “[w]ithout appropriate statutory redefinitions, we believe the proposed rule could allow assignment of jurisdiction of new technologies based solely on FDA preference particularly where it determines the product raises new questions of safety and effectiveness.”<sup>101</sup> The comments of Cook, a large holding company of device manufacturers, urge fidelity to SMDA’s “firm ground rules” for assignment.<sup>102</sup> Cook notes that the agency “must revisit the law and adjust its proposal to effect the efficient, transparent and well-defined process that Congress envisioned.”<sup>103</sup>

These comments imply that the FDA is “stretching” the scope of its jurisdiction to expand its discretion to assign based on factors the commentators judge to be inappropriate under the law. The final rule has not been issued, so it remains to be seen whether the agency will pursue this arguably broader interpretation or if it will retreat in a direction the industry commentators appear to prefer. Whatever the outcome of this effort, however, the pattern documented here holds. In the fourteen years since the first statutory reference to combination products, there have been incremental efforts to respond to new combinations, legislative redefinition of terms, and new procedural directions, and now challenges to the agency’s interpretation of its authority.

#### IV. POLICY ANALYSIS

Combination products continue to present challenges to the regulatory structure of the FDA. How to regulate innovative combinations raises issues that are similar to those that arose

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National Electrical Manufacturers Association, to Food and Drug Administration, Division of Documents Management, Re: Docket No 2004N-0194 (Aug. 17, 2004), at <http://www.fda.gov/ohrms/dockets/dailys/04/aug04/082304/04N-0194-emc00002-01.pdf> (last visited Apr. 19, 2005).

101. Letter from Ronald S. Warren, Executive Director, Smith & Nephew Wound Management, to Food and Drug Administration, Division of Dockets Management, Re: Docket No. 2004N-0194 (Aug. 18, 2004), at <http://www.fda.gov/ohrms/dockets/dailys/04/aug04/082404/04n-0194-c00009-vol1.pdf> (last visited Apr. 19, 2005).

102. Letter from Stephen L. Ferguson, Executive Vice President and Chairman of the Board, Cook Group, Inc., to Food and Drug Administration, Division of Dockets Management, Re: Docket No. 2004N-0194 (Aug. 20, 2004), at <http://www.fda.gov/ohrms/dockets/dailys/04/aug04/082404/04n-0194-c00005-vol1.pdf> (last visited Apr. 19, 2005).

103. *Id.*

around the emergence of innovative drugs, devices, and biologics in the last century. The public policy response to combination products to date has followed predictable patterns. Congress defines the new product and sets specific structures and pathways for the FDA to implement. The FDA interprets its authority, designs regulatory guidelines, through rules, guidances, and other directives. The process is clearly reactive to innovation. It is incremental in approach, focusing on problems that have been identified and experienced, rather than proactive and broad. It is slow by nature. It has been fourteen years since Congress first defined combination products. Since that time, there have been two legislative initiatives and a host of regulatory responses. The rule defining a PMOA is pending. New guidances have recently been issued. Some in industry have called for a re-definition of terms. The process continues.

While the process has been incremental, reactive, and slow, it also has merit in that it is generally predictable. Regulated entities whose efforts to develop new products span years and constitute large investments value predictability in the regulatory process. While the numbers of combination products have remained manageable,<sup>104</sup> it is possible that an onslaught of unique and novel combinations will further challenge the current regulatory scheme. Can the current regulatory process withstand these forces? What are the policy alternatives?

#### A. STATUS QUO APPROACH

The status quo approach involves accepting the traditional historical pattern. One can predict that the FDA will labor to provide guidance on implementation based on what is currently known about combinations. It may try to “stretch” its authority to adapt to uncertainties in the future, such as the effort to design an algorithm for products for which the primary mode of action is not known. Turf battles among the centers will continue. But it is likely that new products will emerge that do not fit the current structure and will challenge the OCP’s efforts. At that point, expect industry to go back to the Congressional drawing board, so to speak, to urge a legislative tweak of the definitions and further refine the terms. If the innovative process accelerates the way some predict, this policy

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104. See OFFICE OF COMBINATION PRODS., *supra* note 12.

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cycle will always be behind the innovation curve. As Dr. Kshitij Mohan, a former FDA official and industry executive noted,

Much of this effort is like measuring length to the fourth decimal place with a crooked ruler. The danger is that the traditional way of dealing with such complexity will make the process even more complex. A new maze of regulations, guidelines, and guidance memos could be the result.<sup>105</sup>

#### B. ALTERNATIVE APPROACHES TO THE STATUS QUO

One alternative to the status quo is to declare that all combination products will follow the regulatory pathway of one of three existing centers. Some medical device innovators have suggested a presumption in favor of the device laws, which they argue are more flexible and adaptable than those that apply to drugs or biologics. Drug or biological expertise could be acquired or imported to CDRH as needed. This solution retains the three centers and allows firm ground rules and predictability by applying one center's jurisdiction. However, given the history of inter-center rivalry, the perception that drug regulation is more protective and CDER has more expertise, and the fact that many combinations are primarily drugs or biologics, there is likely to be resistance to this alternative within the agency and among drug and biologic firms.

Another alternative is to abandon the effort to shoehorn innovations into one of the three silos, pursuant to the SMDA and MDUFMA directives, and create a new Center for Combination Products. This may be a natural extension of the historical pattern and, indeed, new types of products did find their way into new centers over time. Creating a new center would require legislative action. There would be new challenges to overcome with this approach. Deciding what would be the appropriate regulatory pathway would still involve choosing attributes from the various product-specific centers and borrowing or acquiring a broad range of expertise, much of it located elsewhere. Combinations are not as tidily discrete as drugs, devices or biologics. A fourth silo could complicate the process and undermine efforts at predictability. It could also exacerbate the legislative "crazy quilt" with "a bounty of approaches, with each patch of authority a little, or a

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105. Mohan, *supra* note 56, at 2-3.



lot, different from the others.”<sup>106</sup>

### C. ABANDON THE CENTERS CONCEPT

A bolder and clearly controversial step would be to abandon the complex “crazy quilt” of three centers and move to a more flexible approach. This “innovative” approach would allow for adaptation to new products in creative ways. This approach would require a major sea change in the historical relationship of the institutions of government and with the regulated entities.

Congress has traditionally limited FDA discretion through very specific and detailed legislative mandates. The FDA often has been under fire with Congress, although the fire varies depending on the politics of the time. During the debates over the SMDA in the 1980s, former Democratic Congressman Paul Rogers wrote:

[t]he philosophy behind the writing of the Medical Device Amendments was to be so specific in language that less discretion was left to the agency—a first step in the trend in the Congress to make clear that Congress wanted the agencies to follow the Congressional mandate more carefully and not go off on bureaucratic binges pursuing bureaucratic whims.<sup>107</sup>

During the debates over FDAMA in the 1990s, the Republican majority criticized the FDA for not responding more vigorously to industry needs.<sup>108</sup> At various times, both parties have been inclined to distrust agency discretion and guide the FDA with specific and highly detailed legislation. In 2004, Senate Republican Finance Committee Chairman Charles Grassley called for hearings to determine if the FDA was too lax in its oversight of Merck’s drug Vioxx.<sup>109</sup> This is an example of a Republican leader calling the agency to account for alleged laxity in regulatory oversight.

The manufacturers of medical products have not shown an inclination to support agency discretion either. If the comments filed in response to the proposed PMOA rule are any indication, yearnings for flexibility are offset by distrust of the

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106. Horton, *supra* note 14, at 546.

107. Paul G. Rogers, *Medical Device Law — Intent and Implementation*, 36 FOOD DRUG COSM. L.J. 4, 4 (1981).

108. See Peter H. Stone, *Ganging Up on the FDA*, NAT’L J., Feb. 18, 1995, at 410.

109. *Merck Chief is Asked to Testify*, NEW YORK TIMES, Nov. 11, 2004, at C5.

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agency's exercise of discretion. As we discussed earlier, many of the industry comments specifically took the FDA to task for broadly construing its own authority.<sup>110</sup>

Will the FDA press for more discretion? The FDA is a creature of Congress and subject to its oversight. Exercise of discretion can be risky; caution may be its preferred state. On occasion, FDA commissioners have taken risks. Commissioner David Kessler aggressively interpreted FDA authority to regulate tobacco as a drug (and cigarettes as drug delivery devices) during his tenure.<sup>111</sup> He boldly set out to do so and enacted a rule asserting authority to regulate tobacco.<sup>112</sup> The tobacco industry challenged his efforts as outside the scope of the FDA's authority and on other grounds.<sup>113</sup> The U.S. Supreme Court upheld the industry's challenge and the rule was struck down.<sup>114</sup>

The courts have upheld broad FDA discretion, but only when Congress has been silent or ambiguous.<sup>115</sup> Jeffrey E. Shuren, a former FDA official, has forcefully argued for broad FDA discretion.<sup>116</sup> He contends that "courts should grant sufficient deference to agencies' modifications of prior statutory interpretations in order to ensure adequate agency flexibility to meet new challenges within existing statutory delegations of authority."<sup>117</sup>

Congress is not likely to confer broad discretion. Even conservatives and liberals have shown distrust of the FDA. It would take a very creative Congress, supported by a willing industry, and backed by generous judicial interpretations, to change the course of the FDA's history. There is no evidence in

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110. *See supra* note 98.

111. *See* Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco Products to Protect Children and Adolescents, 60 Fed. Reg. 41,314 (proposed Aug. 11, 1995).

112. *See* Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco Products to Protect Children and Adolescents, 61 Fed. Reg. 44,396, 44,400 (Aug. 28, 1996).

113. *See* *Coyne Behm, Inc. v. United States Food and Drug Admin.*, 966 F. Supp. 1374 (M.D.N.C. 1997).

114. *United States Food and Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000).

115. *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 866 (1984).

116. *See* Jeffrey E. Shuren, *The Modern Regulatory Administrative State: A Response to Changing Circumstances*, 38 HARV. J. ON LEGIS. 291, 292 (2001).

117. *Id.*

the past or present to make this option likely.

#### CONCLUSION

At the outset, we asked: “Can Regulation be as Innovative as Science and Technology?” The answer to the question is no. There appears to be little appetite to confer upon the FDA the discretion and flexibility to respond creatively to combination products, or other novel and as yet unforeseen innovations in the future. The history of the FDA is one of iterative, incremental changes through carefully defined legislative distinctions and highly specific regulatory pathways. Politics and administrative law are likely to prevent the FDA from being a bold innovator.

One could argue, however, that our system does not favor innovation in regulatory agencies, even as it is embraced in our scientists and engineers. Innovators and the manufacturers of innovations want regulatory predictability and certainty. They appear to be willing to sacrifice speed and flexibility in exchange. Given the nature of our policy environment and our political preferences, regulators will surely follow the scientific innovators, not lead them.