COMMENTS

Getting a Handle on Hybrid Devices: The FDA and Industries' Struggles with Regulatory Approval of Drug-Eluting Stents and Possible Solutions for Future Combination Devices

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I. INTRODUCTION

> The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
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> The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.[1]

On April 24, 2003, the Food and Drug Administration (FDA) approved the first drug-eluting stent (DES) for use in angioplasty

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1. U.S. Food & Drug Admin., What We Do (May 22, 2009), http://www.fda.gov/AboutFDA/WhatWeDo/default.htm.

procedures in the United States.[2] Cordis Cardiology, a Johnson & Johnson Company, launched this revolutionary medical device weeks later.[3] This was the first major combination device to enter the U.S. market.[4] The excitement that this groundbreaking product generated in the medical community quickly turned to frustration and confusion, as the FDA and medical device makers struggled to fashion a safe, efficient, and timely protocol to bring these novel creations to the hundreds of thousands of patients suffering from coronary artery disease.[5]

First, this Comment will explore the evolution of coronary stents, as well as the structure of the FDA, in order to gain a greater understanding of why DESs turned the FDA approval process upside down. Next, it will examine the obstacles, setbacks, and changes that both the FDA and DES manufacturers experienced over the past six years. Finally, it will propose legislative and administrative solutions that could provide for a safer, more effective, and more efficient route for combination products through the FDA's regulatory process, not only for DESs, but also for the countless combination medical devices that are sure to be developed in the years ahead.

II. BACKGROUND

A. Evolution of Coronary Stents and the Development of the First DES

In 1994, Johnson & Johnson received FDA approval for the first bare metal coronary stent in the United States.[6] Prior to approval of this product, patients with coronary artery disease could either undergo coronary artery bypass surgery, undergo balloon angioplasty, or choose to be treated with medicine alone.[7] Opening a clogged artery with bare metal stents was safer and more effective than balloon angioplasty, less

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2. U.S. Food & Drug Admin., *FDA Approves Drug-Eluting Stent for Clogged Heart Arteries*, FDA NEWS, Apr. 24, 2003, http://www.scienceblog.com/community/older/archives/M/2/fda1403.htm.

3. Johnson & Johnson, *Cordis Develops Cypher Sirolimus-Eluting Coronary Stent*, BIOTECH EQUIPMENT UPDATE, Mar. 1, 2004, http://www.entrepreneur.com/tradejournals/article/113307630.html.

4. Alla Katsnelson, *Biotech's Hidden Stepsister*, SCIENTIST, Oct. 2008, at 33, 35, *available at* 2008 WLNR 19544403.

5. Howard Manresa & Arlen D. Meyers, *Combination Products and the FDA: Issues and Answers*, BIOTECHNOLOGY HEALTHCARE, Feb. 2005, at 41, *available at* http://www.biotechnologyhealthcare.com/journal/fulltext/2/1/BH0201041.pdf.

6. Johnson & Johnson, Cordis Celebrates 50 Years of Transforming Cardiovascular Care (Mar. 26, 2009), http://www.jnj.com/connect/news/all/20090326_090000.

7. Burt Cohen, Drug Eluting Stent Overview (Sept. 2008), http://www.ptca.org/des.html.

intrusive and traumatic than open-heart surgery, and altogether superior to being treated with medication alone.[8] This first coronary stent was basically stainless steel scaffolding that an interventional cardiologist could compress onto an angioplasty balloon in order to route it through a catheter system from the femoral artery around the aortic arch into one of the coronary arteries.[9] Once into the proper coronary artery, the physician positioned the balloon/stent across the lesion in the narrowed vessel.[10] The cardiologist then used a device to inflate the balloon with saline and contrast material in order to expand the balloon and the stent to the proper diameter in order to return the narrowed vessel to its appropriate size.[11] The cardiologist would then deflate and remove the balloon, instantly increasing blood flow to the heart.[12] Today, the mechanics of the procedure remain very much the same.[13]

During the next nine years, the design of the stents improved, and they became increasingly easier to use.[14] The Achilles heel of the bare-metal stents was restenosis.[15] Roughly twenty-five percent of patients treated with these stents returned within six to twelve months with their stents reclogged by scar tissue formation.[16] The trauma that the placement of the stent caused resulted in the vessel "restenosing."[17] The major companies in the stent market in the mid-90s began frantically attempting to develop a solution that would help millions of people worldwide and ensure a windfall for the company first to market.[18] They soon began to develop different drugs that they could load onto these stents that would lessen the effect of the trauma on the arteries in order to maintain greater blood flow and procedural success.[19] The race to market was riddled with regulatory hurdles with which the companies were largely unfamiliar.

After many failed drug/stent combinations and legal battles over the rights to pharmaceuticals that appeared promising, Cordis and Boston

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8. *Id.*

9. George E. Reed Heart Ctr., Westchester Med. Ctr., Interventional Cardiology, Vascular Consultants, http://www.worldclassmedicine.com/body_heart.cfm?id=1393 (last visited Oct. 3, 2009).

10. Coronary Stents, http://www.heartsite.com/html/stent.html (last visited Oct. 22, 2009).

11. *Id.*

12. *Id.*

13. Cohen, *supra* note 7.

14. *Id.*

15. *Id.*

16. *Id.*

17. *Id.*

18. *Id.*

19. *Id.*

Scientific emerged as the frontrunners.[20] Cordis' stent used sirolimus, a pharmaceutical agent used to prevent organ rejection in renal transplants, while Boston Scientific chose paclitaxel, a chemotherapy agent.[21] Both companies used complex polymers to load the drugs onto the stent and time release the agents into the artery walls once deployed.[22] The initial trials in Europe showed zero restenosis in Cordis' version, and excitement in the U.S. medical community grew rapidly.[23] The more complex U.S. trial revealed that the sirolimus stents reduced restenosis to 7.9% compared to 27% in the bare metal control arm.[24] Boston's trials had similar results.[25]

This news was staggering. Almost 500,000 Americans die from coronary heart disease every year.[26] DESs appeared capable of virtually eliminating restenosis and restoring millions of Americans suffering from coronary artery disease to good health.[27] U.S. cardiologists demanded that these stents be made available to their patients immediately.[28] The only obstacle was FDA regulatory approval.

B. Structure and Approval Process of the FDA Pre-DES

In 1938, the Federal Food, Drug, and Cosmetic Act (FDCA) gave the FDA jurisdiction over medical devices.[29] Congress amended this Act in 1976 to create more modern regulatory requirements for devices.[30] In 2002, the legislature passed the Medical Device and User Fee and Modernization Act that created the Center for Devices and Radiological

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20. *Id.*

21. Cheryl A. Thompson, *First Drug-Eluting Coronary Stent Approved*, 60 AM. J. HEALTH-SYS. PHARMACY 1210, 1210 (2003); Taxus Express2 Paclitaxel-Eluting Coronary Stent System: Summary of Safety and Effectiveness (SSED), http://www.accessdata.fda.gov/cdrh_docs/pdf3/P0300255028b.pdf (last visited Sept. 8, 2009).

22. Cohen, *supra* note 7.

23. Press Release, Johnson & Johnson, Zero Restenosis in RAVEL Landmark European Multi-Center Clinical Trial of Cypher Sirolimus-Eluting Stent (Sept. 4, 2001), http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/09-04-2001/0001565160&EDATE=.

24. *News from the Transcatheter Cardiovascular Therapeutics Meeting*, CATH LAB DIG., Oct. 1, 2003, *available at* http://www.cathlabdigest.com/article/2181.

25. *Id.*

26. Ctrs. for Disease Control & Prevention, Heart Disease Facts and Statistics, http://www.cdc.gov/heartDisease/Statistics.htm (last visited Nov. 19, 2009).

27. *See generally News from the Transcatheter Cardiovascular Therapeutics Meeting*, *supra* note 24 (discussing medical trial results for several DESs).

28. John Hall, *Drug-Eluting Stents: The High Cost of Immortality?*, HEALTHCARE PURCHASING NEWS, Aug. 2003, *available at* http://www.findarticles.com (search "high cost of immortality"; then follow first hyperlink).

29. Katsnelson, *supra* note 4.

30. *Id.*

Health Center (CDRH) and the Office of Combination Products (OCP) to help coordinate the approval and regulation of combination products shortly before the approval of Cordis's Sirolimus eluting stent in 2003.[31] The FDA currently has three centers for evaluation of medical products: the Center for Drug Evaluation and Research (CDER), the CDRH, and the Center for Biologics Evaluation and Research (CBER).[32] These three departments are separate and distinct from one another, and each center has its own personnel, regulations, and distinct culture.[33] In large part, the function of the OCP is to decide which center will handle a combination product.[34] When a product is submitted to the FDA for approval, the OCP first assigns the product to one of its three approval centers.[35] It designates the product to one of the centers by determining the product's primary mode of action (PMOA).[36] The PMOA of a product is its essential function.[37] The PMOA of a product is often not apparent and a topic very much open to debate.[38] Determining PMOA can sometimes delay a product significantly.[39] Once the FDA receives the request for designation (RFD) from the manufacturer, they assign the product to one of the three centers after deliberation.[40]

After designation to the appropriate center, the product is subject to the rules and requirements of that division throughout the approval process and after approval has been granted.[41] For example, when a pharmaceutical agent is submitted and subsequently approved, the CDER applies the good manufacturing practices (GMP) standard, whereas when a medical device is submitted, the CDRH applies its own separate and distinct set of standards known as quality system regulation (QSR).[42] Because the centers have developed over the years as independent

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31. *Id.*

32. Kshitij Mohan, *Proposals Currently Before Congress for Changing the Regulation of Products Fall Short of the Needed Reform*, MED. DEVICE & DIAGNOSTIC INDUS., May 1, 2002, *available at* http://www.devicelink.com/mddi/archive/02/05/017.html.

33. *Id.*

34. Erik Swain, *Combination Products: Primary Mode of Action Refined*, MED. DEVICE & DIAGNOSTIC INDUS., Oct. 2005, *available at* http://www.devicelink.com/mddi/archive/05/10/016.html.

35. *Id.*

36. *Id.*

37. *Id.*

38. *Id.*

39. Mohan, *supra* note 32.

40. Stuart Portnoy & Steven Koepke, *Regulatory Strategy: Preclinical Testing of Combination Products*, MED. DEVICE & DIAGNOSTIC INDUS., May 1, 2005, *available at* http://www.devicelink.com/mddi/archive/05/05/028.html.

41. Mohan, *supra* note 32.

42. *Id.*

entities, these types of regulations often differ and even contradict one another.[43] Each center has its own standards for countless requirements including premarket studies, postmarket surveillance, packaging requirements, labeling requirements, off-label promotion prohibitions, etc.[44] The different centers have grown independently and developed their own unique cultures.[45] As funds and resources have always been tight for the FDA, the structure of the system has created somewhat of a rivalry among the centers.[46]

Before 2000, the approval process was much less stringent for medical devices than it was for both drugs and biologics.[47] The most efficient manufacturers were able to secure approval for new bare metal stents in one year.[48] Guidant Corporation, the U.S. stent market leader at the time, secured FDA approval for three different stent generations between 1998 and 2000.[49] Other companies had more difficulty with FDA approval of their stents.[50] Cordis managed to gain only four stent approvals from 1994 to 2000.[51] The difference in the varying approval periods between manufacturers seemed to depend on the proficiency of the company in submitting these products to the FDA, as opposed to any barriers or hurdles in the FDA approval process.[52] The reason that stents could work their way quickly through the FDA was due in large part to the fact that next generation devices were essentially only slight modifications of their predecessors.[53] The clinical trials that the FDA required were much less stringent than for a completely new product.[54] The bare metal stents were seen by the FDA as pure medical devices.

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43. *Id.*
44. Portnoy & Koepke, *supra* note 40; Mohan, *supra* note 32.
45. Mohan, *supra* note 32.
46. *Id.*
47. Katsnelson, *supra* note 4.
48. Press Release, *Guidant Announces FDA Approval of Its MULTI-LINK TETRA Coronary Stent System*, BUS. WIRE, Oct. 3, 2000, http://findarticles.com (search "Guidant TETRA"; then follow first hyperlink).
49. *Id.*
50. Katsnelson, *supra* note 4.
51. Katrina Keller, *Cardiac Comeback*, FORBES.COM, Apr. 30, 2001, http://www.forbes.com/forbes/2001/0430/164.html.
52. Press Release, *supra* note 48.
53. Portnoy & Koepke, *supra* note 40.
54. *Id.*

III. TWO WORLDS COLLIDE

A. FDA Difficulties and Responses to DES

The Cordis Cypher stent was the first major combination product approved by the FDA for commercial use in the U.S. market.[55] The FDA's new practice of assigning products to one of its three main centers for approval was put to the test on a very high profile and public stage.[56] The FDA decided that a DES's PMOA was a device in nature and assigned primary responsibility to the CDRH.[57] DESs, however, rely heavily on the nature and composition of their drug and polymer profiles to establish both safety and efficacy.[58] For this reason, the FDA subjected DESs to many of the standards established by the CDER and CDRH, including both GMP and QSR.[59] The mere fact that DESs were subject to the rules of two FDA centers increased the regulatory approval time considerably.[60] Because these independent centers were largely unfamiliar with collaborative efforts on combination products of this magnitude, further delays resulted.[61] Add in the fact that these departments were sorely understaffed and underfunded, and it is not hard to understand why U.S. market approval occurred two years after European CE mark approval for the Cypher stent.[62]

On March 4, 2004, the FDA approved Boston Scientific's DES Taxus, a paclitaxel eluting coronary stent, only thirteen months after the product received CE mark approval.[63] This timeframe rivaled that of bare metal stent approvals.[64] While the regulatory approval process seemed to be getting more efficient, Medtronic and Guidant were submitting DESs for CE mark approval and planning for FDA submission.[65]

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55. Johnson & Johnson, *supra* note 3.
56. *Id.*
57. Manresa & Meyers, *supra* note 5.
58. *Id.*
59. *Id.*
60. Mohan, *supra* note 32.
61. *Id.*
62. *Id.*
63. U.S. Food & Drug Admin., Taxus Express2 Paclitaxel-Eluting Coronary Stent System-P030025 (June 29, 2009), http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm081189.htm.
64. *Taxus Wins CE Mark as BSX Joins Stent Race*, BBI NEWSLETTER, Feb. 1, 2003, *available at* http://www.accessmylibrary.com/coms2/summary_0286-22549023_ITM.
65. Press Release, Guidant Corp., Guidant Receives European Approval for XIENCE V Drug Eluting Coronary Stent (Jan. 30, 2006), http://www.ptca.org/pr_guidant/20060130.html; Press Release, *Medtronic Receives CE Mark Approval for Endeavor Drug-Eluting Coronary Stent System*, BUS. WIRE, July 31, 2005, *available at* http://findarticles.com (search "Medtronic Endeavor CE Mark"; then follow fourth hyperlink).

Not long after the 2004 approval of Taxus, the FDA (CDER specifically) came under increased scrutiny after drugs that it "fast tracked" through the approval process were recalled for safety concerns.[66] On September 30, 2004, Merck recalled their blockbuster anti-inflammatory drug Vioxx.[67] The CDER acknowledged that they received studies from Merck in 2000 that showed an increase in cardiac events, including myocardial infarction and stroke, when compared with naproxen, a competing drug.[68] Dr. Sandra Kweder, deputy director of the Office of New Drugs at the FDA, admitted that the agency "took too long to get information about Vioxx's heart risks into the prescribing label that is provided to physicians."[69] A multiple sclerosis drug called Tysbari was also removed from the market that same year for safety concerns.[70] Concerns began to arise about the FDA's accelerated approval process for breakthrough drugs.[71] The FDA was under intense public and political scrutiny.[72] Senator Michael Enzi, who was chairman of the health committee at the time, said that examining the problems at the FDA "was 'not only critical, but it's also a hot issue right now.'"[73] Faced with severe political and public scrutiny, the FDA was undoubtedly wary of making another misstep.

Growing concerns about the safety profile of DESs did not help matters. In 2005, a European study suggested that DESs caused an increased rate of potentially fatal blood clots.[74] The FDA was once again faced with a situation where it appeared that it may have rushed a product to market. The FDA did not recall either of the two DESs on the market for stent thrombosis.[75] While some in the medical community harbored concern and uncertainty over the safety profile of DESs, others thought that it was a natural consequence of DES use in complex patient

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66. U.S. Food & Drug Admin., *Merck Withdraws Vioxx; FDA Issues Public Health Advisory*, FDA CONSUMER MAG., Nov.-Dec. 2004, at 11.

67. *Id.*

68. *Id.*

69. Gardiner Harris, *F.D.A. Official Admits 'Lapses' on Vioxx*, N.Y. TIMES, Mar. 2, 2005, *available at* http://www.nytimes.com/2005/03/02/politics/02fda.html.

70. Ricardo Alonso-Zaldivar, *Warning Didn't Slow Approval of MS Drug*, L.A. TIMES, Mar. 2, 2005, *available at* http://articles.latimes.com/2005/mar/02/business/fi-biogen2.

71. *Id.*

72. *Id.*

73. Harris, *supra* note 69.

74. Alfredo E. Rodriguez, *Coronary Stent Thrombosis in the Current Drug-Eluting Stent Era: Insights from the ERACI III Trial*, J. AM. C. CARDIOLOGY, Dec. 13, 2005, at 205, 207 *available at* http://content.onlinejacc.org/cgi/reprint/47/1/205.

75. *FDA Panel Provides Cautious Support for Drug-Eluting Stents*, MX BUS. STRATEGIES FOR MED. TECH. EXECUTIVES (Dec. 2006), http://www.devicelink.com/mx/issuesupdate/06/12/DESPanel.html.

populations or under-deployment of the stent.[76] Many still thought that there was no legitimate safety issue with DESs.[77]

The FDA did not approve another DES until 2008.[78] Medtronic received FDA approval for its Endeavor everolimus eluting stent on February 1, 2008, two and a half years after receiving CE mark approval.[79] Similarly, Abbott, who purchased Guidant's coronary stent division in 2006, received FDA approval for its XIENCE DES on July 2, 2008, nearly two and a half years after receiving European approval on January 30, 2006.[80]

It cannot go without notice however, that six years after FDA approval of Cypher, Cordis has yet to receive FDA approval for a second generation device.[81] Boston Scientific, on the other hand, received FDA approval for Taxus Liberte, its second generation DES in 2008, more than four years after approval of their first DES.[82] Europe, however, approved Boston Scientific's second generation DES in 2005 and Cordis's third generation DES in 2006.[83] Both companies have attempted to gain approval for next generation devices that contained the same drug/polymer combination on altered stent designs in the United States under the impression that the requirements for second generation DES approval would be less severe.[84]

Essentially, the only difference in the next generation products is the design of the stent device.[85] The FDA, however, believes that there could be an unintended adverse effect due to the change in the pattern of

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76. *Id.*

77. *Positive Studies Boost Stent Manufacturers as Market Competition Heats Up*, MX BUS. STRATEGIES FOR MED. TECH. EXECUTIVES (Apr. 2008), http://www.devicelink.com/mx/issuesupdate/08/04/Stents.html.

78. George E. Jordan, *Outlook for Stents Improving: Makers Optimistic Data, Device Can Revive Sales*, NEWARK STAR LEDGER, Mar. 5, 2008, at 21, *available at* http://www.nj.com/business/index.ssf/2008/03/outlook_for_stents_improves.html.

79. Press Release, Medtronic, Inc., FDA Approves Medtronic's Drug-Eluting Stent (Feb. 1, 2008), http://www.ptca.org/news/2008/0201_MEDTRONIC.html.

80. Press Release, Abbott, FDA Approves Abbott's XIENCE V Drug Eluting Stent (July 2, 2008), http://www.abbott.com/global/url/pressRelease/en_US/60.5:5/Press_Release_0623.htm.

81. Cordis, Cordis CYPHER® Sirolimus-Eluting Coronary Stent, http://www.cordis.com/products/cypher-sirolimus-eluting-coronary-stent (last visited Nov. 19, 2009).

82. Press Release, Frost & Sullivan, Frost & Sullivan Recognizes Boston Scientific with Stent Market Leadership Award (Nov. 28, 2008), http://www.frost.com/prod/servlet/press-release.pag?docid=149076806.

83. *Cordis's Third-Generation Coronary Stent Gets CE Mark Approval*, BIOTECH EQUIP. UPDATE, Aug. 1, 2006, http://www.entrepreneur.com/tradejournals/article/148365546.html.

84. Shelley Wood, *Next Generation Drug Eluting Stents Tackle Shortcomings in Cypher, Taxus*, HEARTWIRE, Feb. 7, 2006, http://www.theheart.org/article/641591.do.

85. *Id.*

delivery.[86] This seems to be its rationale for maintaining very stringent requirements for approval of next generation DESs.[87]

The FDA has made some efforts to reduce review times for DESs.[88] In 2006, the CDRH launched an initiative to "promote early interaction between the FDA and industry to optimize review times and foster innovation."[89] Part of its plan was to develop and issue specific guidance on complex medical devices like DESs.[90] The initiative promised to "outline scientific, clinical and technical issues that should be considered early in the development process."[91] It also vowed to modernize its review process for innovative devices by improving the training of the reviewers and using information technology to improve communication and make the approval process more efficient.[92]

In 2008, the FDA issued draft guidance to the coronary DES industry on the regulatory approval process for comment.[93] This guidance did not contain any mandates or responsibilities; it simply made suggestions to the industry.[94] The drafters of this guidance repeatedly stressed that this document contained only the FDA's current thinking on the topic and did not affect the rights or responsibilities of anyone.[95] The fact that the FDA signaled that it did not intend to promulgate a rule that affected individual rights was significant.[96] If the FDA truly intended this document to be purely guidance, then the notice and comment procedure was not required. The FDA did, however, put the guidance out for comment and filed it with the Federal Register.[97] This could be a signal that the agency has a legitimate interest in working with industry to solve the DES regulatory issues. On the other hand, the FDA is required by the FDCA to utilize formal rulemaking procedures when promulgating

86. U.S. FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: CORONARY DRUG ELUTING STENTS—NONCLINICAL AND CLINICAL STUDIES COMPANION DOCUMENT (Mar. 2008), *available at* www.fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/Guidances/UCM072196.pdf.

87. *Id.*

88. U.S. FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., MEDICAL DEVICE INNOVATION INITIATIVE (May 2006), *available at* http://www.fda.gov/AboutFDA/Centers Offices/CDRH/CDRHInitiatives/ucm118252.htm.

89. Press Release, U.S. Food & Drug Admin., FDA Announces Initiative To Facilitate the Development and Availability of Medical Devices (May 22, 2006), http://www.fda.gov/News Events/Newsroom/PressAnnouncements/2006/ucm108658.htm.

90. U.S. FOOD & DRUG ADMIN., *supra* note 88.

91. *Id.*

92. *Id.*

93. U.S. FOOD & DRUG ADMIN., *supra* note 86.

94. *Id.*

95. *Id.*

96. *Id.*

97. *Id.*

regulations such as these.[98] As the FDA is very reluctant to deviate from its guidance documents, this document could be seen as having the effect of law and the fact that the agency put the guidance out for notice and comment could be an attempt to legitimize the process.[99]

The draft guidance outlined the agency's current views on topics pertaining to DES approval and all aspects of regulation.[100] Basically, it walked through the entire approval process and attempted to make clear the agency's thoughts and expectations on every aspect of DES approval.[101] It covered product development pathways, clinical and nonclinical studies, manufacturing practices, clinical trial planning and design, post-approval studies and reporting, and many other issues pertinent to DES approval in painstaking detail.[102] Although the final guidance has yet to be published, the draft guidance seems to be an excellent step towards opening the lines of communication between the FDA and the DES industry.

B. Industries' Difficulties and Response to FDA

DES manufacturers' struggles stemmed from the fact that they were swimming in uncharted waters. These medical device companies were largely unfamiliar with CDER requirements and failed to anticipate FDA expectations in many regards.[103]

Other than the apparent delays in DES approvals, it is difficult to know the exact preapproval struggles of the manufacturers, but their postapproval problems were immediately apparent. The first and easily the biggest blunder belonged to Cordis.[104] Cordis mistakenly believed that it submitted enough evidence and data for the FDA to approve Cypher with a one-year shelf life similar to its CE Mark approval.[105] The FDA, however, granted Cordis a six-month shelf life that Cordis later reduced to three months.[106] The impact of this misstep was devastating.[107]

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98. 21 U.S.C. § 371 (2006).

99. Food and Drug Administration's Development, Issuance, and Use of Guidance Documents, 62 Fed. Reg. 8961, 8963 (Feb. 27, 1997).

100. U.S. Food & Drug Admin., *supra* note 86.

101. *Id.*

102. *Id.*

103. Mohan, *supra* note 32.

104. Ross Kerberand & Jeffrey Krasner, *Johnson & Johnson Missing Out on Stent Sales*, BOSTON GLOBE, Aug. 19, 2004, at E1, *available at* http://www.boston.com/business/articles/2004/08/19/johnson__johnson_missing_out_on_stent_sales/.

105. Shelly Wood, Rocky Rollout of Cypher Stent Has Produced Picky Patients and Rumors of Rumbles Between Physicians Vying for Short Supplies, HEARTWIRE, June 6, 2003, *available at* http://www.theheart.org/article/251053.do.

106. Kerberand & Krasner, *supra* note 104.

Because of the unexpectedly short dating, Cordis could not produce enough DESs to supply the entire market.[108] When it launched Cypher, only certain hospitals were allowed to purchase Cypher, and only in limited quantities.[109] Cordis's manufacturing capability improved, but it was never able to supply the entire DES market consistently due to its mistaken belief that the FDA would grant it a longer shelf life.[110] Even during the times it could supply the market, Cordis was losing massive amounts of inventory to expiration.[111] This failure drew the wrath of most of the medical community and cost the company hundreds of millions of dollars in lost sales.[112] Cordis has had continuous problems because of the relatively short shelf life of their DES.[113]

Cordis soon learned the difficulty of complying with both the CDER's GMPs for drugs and CDRH's QSRs for devices. On March 1, 2004, the FDA reprimanded Cordis with a warning letter detailing deficiencies in design, manufacture, and distribution of their DES after inspections of facilities in Miami, Puerto Rico, the Netherlands, Belgium, Mexico, and Italy.[114] The FDA cited a myriad of defects at these plants, including a failure to comply with the CDER's GMPs, a set of standards that was not applied to bare metal stents.[115] The report also noted failures to establish and maintain adequate procedures for corrective and preventive actions, among other items.[116] If medical companies do not take corrective measures after receiving a warning letter, the FDA can take extreme regulatory action, including seizing product, issuing court injunctions against further production, and imposing civil monetary damages.[117] The mere issuance of a warning letter will also slow the approval of any devices the company has pending.[118] The FDA lifted this warning letter in June 2007.[119]

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107. *Id.*
108. *Id.*
109. Hall, *supra* note 28.
110. *Id.*
111. Kerberand & Krasner, *supra* note 104.
112. *Id.*
113. Hall, *supra* note 28.
114. *Cordis Fails Six-Site, Post-Approval Inspection*, VALIDATION TIMES, Apr. 1, 2004, *available at* 2004 WLNR 22295817.
115. *Id.*
116. *Id.*
117. *FDA Cites Boston Scientific Twice in August*, GMP LETTER, Sept. 26, 2005, *available at* 2005 WL 25588496.
118. *FDA Approves Boston Scientific's Next Generation Version of Taxus Drug-Coated Stent*, INVESTREND, Oct. 13, 2008, 2008 WLNR 19487591.
119. *Reports Highlight Recent Developments from Cordis Corporation*, HEALTH & MED. WEEK, July 23, 2007, *available at* 2007 WLNR 13807087.

Boston Scientific experienced similar compliance-related problems.[120] In August 2005, the FDA issued a warning letter to Boston Scientific concerning its DES facilities.[121] One of the more egregious violations was the shipment of eight DESs that failed a kinetic drug-release test.[122] The FDA remarked that the numerous violations "may be symptomatic of serious underlying problems in [the] establishment's quality system."[123] Boston came into compliance and the FDA lifted the warning letter in 2008.[124]

The poor manufacturing processes of both companies did not escape congressional scrutiny.[125] In August 2007, the House Energy and Commerce Committee launched an investigation to determine why the FDA did not recall both companies' stents after the failures at the production facilities.[126] This was not the first time that the FDA and these two companies were under congressional review.[127] In March 2007, the House Oversight and Government Reform Committee requested data from Cordis and Boston Scientific about DES clinical trials.[128] The Committee expressed specific concern that the companies were promoting DESs for use in off-label procedures or situations in which the FDA had not specifically approved DESs for use, like in-stent restenosis, myocardial infarction, and other complex cases.[129] Their concern stemmed from information suggesting that the reported increase in blood clots with DESs was directly related to off-label use.[130]

C. Who Is To Blame?

In light of the tremendous difficulties in approval and postmarket compliance of the first major drug/device combination products brought to the U.S. market, there is considerable fault to be distributed. The DES industry, the FDA, and Congress all bear significant blame.

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120. *FDA Cites Boston Scientific Twice in August*, *supra* note 117.

121. *Id.*

122. *Id.*

123. *Id.*

124. *FDA Approves Boston Scientific's Next Generation Version of Taxus Drug-Coated Stent*, *supra* note 118.

125. David Filmore, *Lawmakers Probe FDA over Handling of Cordis Warning Letter*, GRAY SHEET, Aug. 20, 2007, *available at* http://www.medicaldevicestoday.com/2007/08/lawmakers-probe.html.

126. *Id.*

127. *House Panel Chief Seeks Data from Makers of Stents and Drugs*, N.Y. TIMES, Mar. 6, 2007, *available at* http://www.nytimes.com (expand search to "All Results Since 1851"; search "panel"; then "drug-coated stents" and follow second link).

128. *Id.*

129. *Id.*

130. *Id.*

Although the DES manufacturers had not dealt with the CDER regularly, they certainly had to know that the combination of a time-released drug and polymer would surely bear more scrutiny than their previously approved bare metal stents. Although their DES products faced significantly fewer hurdles gaining CE mark approval, the companies should have anticipated much greater resistance in the United States. Devices and drugs historically have been approved much sooner and with fewer requirements overseas, and the unique, if not inept, structure of the FDA should have put the companies on notice that they would have to meet most, if not all, of the requirements of drug approval in the CDER as well as device approval in the CDRH. They also should have realized that the FDA would subject DESs to the more stringent CDER manufacturing and labeling requirements for drugs. The DES manufacturers should have anticipated meeting both centers' requirements and made every effort to clarify discrepancies in advance of their clinical trials and production. The fact that Cordis failed to provide the FDA with enough information to justify more than a six-month expiration date is inexplicable.[131] Both Cordis and Boston Scientific experienced significant delays in DES approval and were also reprimanded by the FDA for maintaining inadequate manufacturing processes that resulted in further delays to their next generation DESs.[132] The fact that the companies were bringing one of the most revolutionary and lucrative medical technologies in history to market should have warranted a more detailed plan.[133] Their lack of foresight, planning, and execution cost their companies and shareholders hundreds of millions of dollars and deprived the public of a lifesaving technology during the delays in approval.[134]

The FDA is not without blame for the DES debacle. While the FDA draft guidance contains very detailed instruction for testing, submission, manufacturing, and postmarket surveillance activities, it was circulated for comment five years after the U.S. approval of the first DES.[135] Certainly, the agency could have put out information that they term as "nonbinding recommendations" before three different companies brought a DES to market.[136] While this information appears to be very helpful going forward, Cordis would have found this information even

131. Kerberand & Krasner, *supra* note 104.
132. Hall, *supra* note 28.
133. *See id.*
134. *Id.*
135. U.S. Food & Drug Admin., *supra* note 86.
136. *Id.*

more useful in the late 1990s when it began clinical trials for Cypher. Without published guidance, the first DES companies to market were left largely in the dark. The lack of regulations or guidance issued by the FDA contributed greatly to the troubles associated with the launch of DESs in the United States.

Congress may be the root of the problem because it is responsible for the structure and funding of the FDA. The fact that the CDER and CDRH are separate and distinct agencies with their own unique culture, personnel, and regulations hinders the approval process of combination products.[137] By its very nature, the structure of the FDA, in this respect, is ill-suited to handle combination devices. Although the FDA designated CDRH as the lead center in the approval of DESs, both centers played a significant role in the approval process.[138] This interplay between different centers could only have added to the confusion.

Congress alone is responsible for funding the FDA. The FDA is undermanned, underfunded, and the personnel turnover rate is high.[139] Tasked with ensuring the safety and efficacy of drugs and devices, the CDER and CDRH faced a very daunting task in ensuring the safety and efficacy of DESs in a collaborative effort.[140]

IV. SOLUTIONS GOING FORWARD

Difficulties with the approval and regulation of combination products are certain to grow in the years to come.[141] In 2007, the FDA received 333 applications for combination product approval, a forty-two percent increase over the previous year.[142] In addition to the increased volume of combination products flowing into the FDA, these hybrids are sure to evolve into even more complex products.[143] Abbott, for example, is currently conducting clinical trials to evaluate the safety and efficacy of a fully bioabsorbable DES.[144] As more companies develop therapeutic products that contain a combination of drugs, devices, and biologics, the puzzle will certainly magnify in complexity. In order for the FDA to

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137. Mohan, *supra* note 32.

138. *Id.*

139. *Id.*

140. *Id.*

141. *Biggest Challenge for Combination Products Is Quality Control*, GMP LETTER, Dec. 3, 2008, *available at* 2008 WLNR 24025036.

142. *Id.*

143. *Id.*

144. *Abbott Advances Fully Bioabsorbable DES with Next Phase of Clinical Trial*, DIAGNOSTIC & INVASIVE CARDIOLOGY, Mar. 24, 2009, *available at* http://www.dicardiology.net/node/31707.

effectively ensure the safety and efficacy of combination products and deliver these lifesaving inventions to the American people in a timely manner, Congress must take decisive action.

First, Congress should create a new branch of the FDA solely responsible for the approval and regulation of combination products. The FDA could create a task force to create this new center with leaders from each of the three branches who would join the center and recruit a team of scientists and personnel to man the new Center for Combination Products (CCP). Certainly the creation of a new center will have growing pains, but it seems a necessary step to address the onslaught of combination products in the coming years. Once formed, the OCP could simply make the determination of whether a product was a drug, device, biologic, or combination and designate it to the appropriate center. The new center would make the PMOA determination process much easier for the OCP. If the PMOA is unclear, then the OCR could send the product to the CCP, which would be capable of handling any type of product or combination thereof. The CCP would eventually be able to handle all of the approval and regulatory functions concerning combination products without consulting other centers. This autonomy would create a much more effective and efficient approval and regulatory process.

Congress should enact legislation that would grant the CCP full authority over the approval and regulation of combination products and also ensure that the CCP is appropriately staffed and funded. This legislation would certainly prove very costly, but the bulk of the funds should not come from the national budget. In 2007, President George Bush signed an act reauthorizing medical device user fees.[145] These fees account for much of the FDA's operating expenses.[146] This act significantly reduced the amount of fees that the FDA collects from companies seeking device approval.[147] Congress should include in its legislation creating the CCP similar increased fees for the approval of combination products in order to subsidize the creation of the CCP. The creation of this new center would benefit combination product companies by reducing the time of new combination product approval, thereby decreasing the cost of getting new products approved through a

145. U.S. FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., MEDICAL DEVICE USER FEES HAVE BEEN REAUTHORIZED FOR FISCAL YEARS 2008-2012 (Sept. 28, 2007), *available at* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109089.htm.

146. *Id.*

147. *Id.*

more efficient system and increasing company profits by bringing their products to market sooner.

The advent of DESs revealed that the current structure of the FDA is ill equipped to handle complex combination devices. Minor changes to an obsolete system will prove ineffective in the approval and regulation of more complex future combination products. It is imperative that Congress enact legislation to create a well-funded CCP to ensure that Americans receive the most technologically advanced treatments available in a safe and timely manner.