FOOD AND DRUG LAW JOURNAL

Analyzing the Laws, Regulations, and Policies Affecting FDA-Regulated Products

Bringing Smart Pills to Market: FDA Regulation of Ingestible Drug/Device Combination Products

Matthew Avery
Dan Liu

FDLI

VOLUME 66 NUMBER 3 2011

Bringing Smart Pills to Market: FDA Regulation of Ingestible Drug/Device Combination Products

MATTHEW AVERY
DAN LIU*

INTRODUCTION

The pharmaceutical industry is under siege, with revenue threatened by rising research and development costs, a shrinking product pipeline, and relentless challenges from generic manufacturers. Since peaking in 1996, when the Food and Drug Administration (FDA) approved 53 new drugs, the annual number of new drugs approved for marketing has steadily declined.[1] Only 21 new drugs were approved by FDA in 2010.[2] Over the same period, research and development spending by pharmaceutical manufacturers has increased 187 percent, from $16.9 billion to $48.5 billion.[3] Compounding this problem is a rapidly approaching "patent cliff."[4] In the past three years, more than 70 drugs have gone off patent.[5] By the year 2014, nine of the top-15 best-selling drugs in the world will lose patent protection.[6] And generic companies continue to file hundreds of applications each year to market generic versions of these brand-name drugs, with approximately 850 such applications filed in 2010 alone.[7] All these factors suggest that the pharmaceutical industry is poorly prepared for dealing with these threats.

In response to these challenges, the pharmaceutical industry has turned away from traditional areas of development to search for new solutions.[8] Some companies have attempted to lengthen the lifetimes of their products with new formulations,

* Mr. Avery is an Associate at Baker Botts LLP in Palo Alto, California. Dr. Liu is a J.D. Candidate at the University of California, Hastings College of the Law, 2012. The authors would like to thank Professors Robin Feldman and Marsha Cohen of U.C. Hastings for advising them on this Article as part of the U.C. Hastings Law and Biosciences (LAB) Project.

1 *See* BURRILL & CO., BIOTECH 2008 LIFE SCIENCES: A 20/20 VISION TO 2030, at 43 (2008); Matthew Arnold, *FDA BLA Approvals Rose in 2009 While NMEs Stumbled*, MED. MARKETING & MEDIA, Dec. 31, 2009, http://www.mmm-online.com/fda-bla-approvals-rose-in-2009-while-nmes-stumbled/article/160496/; Matthew Avery, *Personalized Medicine and Rescuing "Unsafe" Drugs with Pharmacogenomics: A Regulatory Perspective*, 65 FOOD & DRUG L.J. 37, 38 (2010); *Pills Get Smart: Potential Encapsulated*, ECONOMIST, Jan. 14, 2010, http://www.economist.com/businessfinance/displayStory.cfm?story_id=15276730.

2 *See* Jennifer Corbett Dooren, *Drug Approvals Slipped in 2010*, WALL ST. J., Dec. 31, 2010, http://online.wsj.com/article/SB10001424052748704543004576052170335871018.html.

3 *See* Avery, *supra* note 1, at 38.

4 *See* Christopher K. Hepp, *Big Pharma Gearing up to Face the Patent Cliff*, PHILA. INQUIRER, Nov. 12, 2010, http://www.philly.com/inquirer/business/107412428.html; *More Than 1,000 Drug Patents Expiring During the Next Two Years*, PHARMALIVE, Dec. 3, 2010, http://www.pharmalive.com/News/index.cfm?articleid=747957&categoryid=32.

5 *See* David Collis & Troy Smith, *Strategy in the Twenty-First Century Pharmaceutical Industry: Merck & Co. and Pfizer Inc.*, Harvard Business School, November 16, 2007. One group reported that nine of the top ten biggest drugs in the world will lose patent protect by 2014. *See* Hepp, *supra* note 4.

6 *See* Tom Randall, *Drugmakers Poised to Report Biggest Drop Since 2006 on Record Patent Loss, Bloomberg.com,* Apr. 15, 2011, *http://www.bloomberg.com/news/2011-04-15/drugmakers-poised-to-report-biggest-drop-since-2006-on-record-patent-loss.html.*

7 *See* Kurt R. Karst, *OGD Finished 2010 on a High Note – Really High!*, FDA LAW BLOG, Feb. 3, 2011, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2011/02/ogd-finished-2010-on-a-high-note-really-high.html.

8 *See Pills Get Smart*, *supra* note 1.

such as "extended release" or other minor variations of existing drugs.[9] Others have turned to developing "me too" drugs, which are new drugs that have a chemical composition that is almost identical to an existing drug.[10] But these techniques cannot always be used, and consumers are beginning to tire of "new" drugs that provide little value over drugs that are already on the market.

Now some pharmaceutical manufacturers are turning to "smart pill" technology.[11] Despite the name, these are not pills for making patients more intelligent. Rather, these pills function more smartly than traditional drugs. An example of a smart pill is an oral tablet that incorporates some type of medical device, such as a microchip, that controls the release of the active pharmaceutical ingredient after ingestion.[12] Smart pills may be able to improve the safety or effectiveness of an existing drug with targeted delivery, controlled drug release, compliance monitoring, and other benefits.[13] Furthermore, these new products may generate new patents, allowing manufacturers to thwart generic competition.

However, developers of smart pills face major regulatory challenges. Drugs and medical devices are regulated by different branches within FDA, and each branch has a distinct regulatory process. While a smart pill is neither purely a drug nor purely a medical device, from FDA's perspective a smart pill is *both* a drug and a medical device. The agency would designate a smart pill as a combination product, which is part of the problem. The regulation of combination products is relatively new and unexplored territory for FDA.[14] Consequently, sponsors may be hesitant to develop smart pills because it is not clear how FDA will regulate this new technology. Moreover, FDA's inconsistent designation results and burdensome manufacturing requirements further discourage the development of such products.[15]

Another challenge for smart pill developers is that the regulation of their products may be overseen by a sub-agency within FDA that is poorly equipped to analyze the safety and efficacy of the novel features of the smart pill. FDA determines how a combination product is regulated based on its "primary mode of action."[16] A combination product that functions primarily as a drug is regulated as a drug, while a combination product that functions primarily as a medical device is regulated as a

[9] *See* Collis & Smith, *supra* note 5.

[10] *Id.*

[11] *See Pills Get Smart*, *supra* note 1.

[12] *See* Ben Hirschler, *Look Out, Your Medicine Is Watching You*, REUTERS, Nov. 8, 2010, http://www.reuters.com/article/idUSTRE6A754720101108.

[13] *See Pills Get Smart*, *supra* note 1.

[14] FDA's Office of Combination Products reviews approximately 300 products per year. *See* FDA, FY 2008 PERFORMANCE REPORT TO CONGRESS FOR THE OFFICE OF COMBINATION PRODUCTS, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/PerformanceReports/CombinationProducts/UCM214648.pdf. However, the vast majority of these products are trivial combinations, like prefilled syringes, or minor variations of approved drug-eluting stents. Very few of these products are novel products or product-combinations.

[15] GMP Letter, *Proposed Combo Product GMPs May Pose a Big Cost Burden*, Jan. 8, 2010, 2010 WLNR 364192.

[16] *See* Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16, 104 Stat. 4511 (codified at 21 U.S.C. § 353(g)); 70 Fed. Reg. 49,848 (Aug. 25, 2005); Assignment of Agency Component for Review of Premarket Applications, 56 Fed. Reg. 58,754, 58,574 (Nov. 21 1991) (codified at 21 C.F.R. pt. 3). Note that this article uses "efficacy" and "effectiveness" interchangeably, though the Authors acknowledges that "effectiveness" is the preferred term of art. Interview with Peter Barton Hutt, Senior Counsel, Covington & Burling LLP, in Wash., D.C. (Feb. 13, 2009); *see also* DEP'T OF HEALTH & HUMAN SERVICES, SECRETARY'S ADVISORY COMM. ON GENETICS, HEALTH & SOC'Y, REALIZING THE POTENTIAL OF PHARMACOGENOMICS 34 n.234 (2008) ("[T]he term 'effectiveness' is used as a measure of how well the test performs in 'real-world' clinical settings, and 'efficacy' is used for outcomes seen in controlled research settings.").

device.[17] Most smart pills function primarily as drugs, and thus would be regulated by FDA's Center for Drug Evaluation and Research (CDER). However, the novel aspects of many smart pills are the devices that are incorporated with the drugs, and CDER is ill-equipped to analyze whether these devices are safe and effective.

This article predicts how FDA will regulate smart pills and shows how the current regulatory regime is flawed. Part I of this article provides a brief overview of smart pills and the regulatory factors that deter the development of smart pills. Part II reviews FDA regulation of combination products generally. Part III then predicts how FDA will apply its regulations to ingestible drug/device combination products seeking marketing approval. This section will also show how current regulations are inadequate for addressing the challenges of developing smart pills, and how FDA's current regulations discourage such development. Finally, Part IV proposes that FDA can encourage development of smart pills by (1) regulating combination products based on their "novel mode of action" rather than their "primary mode of action," (2) creating a marketing approval pathway specifically for combination products, and (3) eliminating regulations that require sponsors to get marketing approval from multiple centers within FDA and providing regulatory guidance specifically for ingestible drug/device combination products.[18]

I. OVERVIEW OF SMART PILLS

A. *The Science of Smart Pills*

The term "smart pill" refers to an ingestible drug equipped with drug-delivery technology.[19] Some smart pills are designed to monitor and control drug release. Others are designed to record data related to drug release, including when, where, and how much of the drug is released, as well as temperatures and heart rates.[20] These technologies offer therapeutic advantages over their conventional counterparts in several ways. First, delivering a drug at the precise location and releasing it at the right time can improve the effectiveness and reduce the toxicity of the drug.[21] Second, knowing whether a drug has been taken can benefit patients by improving treatment compliance.[22] Third, since the information can be transmitted to external devices, both patients and healthcare providers can be empowered to make better decisions based on the drug delivery results.[23]

---

[17] *See* FDA, INTERCENTER AGREEMENT BETWEEN THE CENTER FOR DRUG EVALUATION AND RESEARCH AND THE CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, at VIII.B.2 (2006), http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121177.htm; 21 U.S.C. § 301(g)(1), 301(h).

[18] It is beyond the scope of this article to analyze the following issues related to smart pills: (1) data privacy issues related to the transmission of data to and from smart pills, and (2) post-marketing regulatory requirements for smart pills. For a discussion of data privacy issues, *see generally* Hirschler, *supra* note 12.

[19] *See Pills Get Smart*, *supra* note 1; PHILIPS, *IntelliCap: How It Works*, http://www.research.philips.com/initiatives/intellicap/tech-howworks.html (last visited Jan. 16, 2011).

[20] *See* PHILIPS, *supra* note 19.

[21] *Id.*

[22] *See Pills Get Smart*, *supra* note 1 (arguing that failing to take prescription drugs as directed leads to poor health). Here, treatment compliance refers to the degree to which a patient correctly follows a course of medical advice, e.g., taking a prescribed pill three times per day.

[23] *See* Jo Macfarlane, *Microchip that tells the GP if you've taken your pills*, DAILYMAIL.CO.UK (Apr. 12, 2009 2:35 AM), http://www.dailymail.co.uk/health/article-1169305/Microchip-tells-GP-8217-ve-taken-pills.html.

A prime example of smart-pill technology is the Raisin System developed by Proteus Biomedical, an emerging California-based medical device company.[24] The Raisin is an edible, biocompatible microchip that can be combined with any conventional drug.[25] As the drug is digested in the stomach, the microchip generates an electric charge that is detected by a sensing patch on the patient's skin.[26] The skin patch can monitor compliance by recording the time and date that the pill is digested. The skin patch can also measure some vital signs, such as the patient's heart rate, activity, and respiration.[27] The sensing patch can transmit this information to the patient or his physician for review and analysis.[28] Patients can then be reminded to take missing doses and physicians can more closely monitor patient care, both of which help improve the quality of treatment.[29]

The Raisin microchip is only one-millimeter wide and is invisible to patients.[30] Each microchip sensor only costs a few cents to manufacture and could likely be incorporated into any pill during the typical manufacturing process.[31] Therefore, a Raisin-powered smart pill may be an appealing alternative to a conventional drug because of the useful features, the wide compatibility with other drugs, and the low manufacturing cost. Proteus is bullish on the potential for the technology and believes it "will help create a $100 billion industry."[32]

In August 2010, the Raisin System received a CE mark, allowing Proteus to begin marketing the device in the European Union.[33] The Raisin System is currently being studied in human clinical trials in the United Kingdom.[34] Proteus recently granted an exclusive worldwide license to use the Raisin technology in organ transplantation applications to Novartis, the Swiss pharmaceutical giant. Novartis has announced that it plans to seek regulatory approval for its first Raisin-powered smart pill by mid-2012, demonstrating the drug industry's strong interest in this new technology.[35]

Other companies are also developing smart pills technology. For example, Philips, a multinational electronics company, announced in 2008 that it was developing a new smart pill technology called "iPill," an electronic capsule capable of controlled drug delivery.[36] However, Proteus, Philips, and other smart pill developers face a variety of economic and regulatory barriers that may delay or prevent their innovative products from ever reaching patients.[37]

---

[24] *See* PROTEUS BIOMEDICAL, *Technology*, http://www.proteusbiomed.com/technology/*; Pills Get Smart, supra* note 1.

[25] *See* Brian Dolan, *Proteus: China Likely to Swallow "Smart Pills" First*, MOBIHEALTHNEWS (June 11, 2009, 03:21PM), http://mobihealthnews.com/2688/proteus-biomedical-china-likely-to-swallow-smart-pills-first/.

[26] *Id.*

[27] *Id.*

[28] *Id.*

[29] *See* Brian Dolan, *CTIA Proteus Biomedical: A $100B industry*, MOBIHEALTHNEWS (Apr. 9, 2009, 01:10AM), http://mobihealthnews.com/1314/ctia-proteus-biomedical-a-100b-industry/.

[30] *See* Macfarlane, *supra* note 23.

[31] *See* PROTEUS BIOMEDICAL, *supra* note 24; Macfarlane, *supra* note 23.

[32] *See* Dolan, *supra* note 25.

[33] *See* PROTEUS BIOMEDICAL, *News*, http://www.proteusbiomed.com/2010/08/13/proteus-biomedical-announces-european-ce-mark-approval-of-ingestible-sensor-and-monitor-system/ (2010).

[34] *See* Andrew Kessel, *Proteus Ingestible Microchip Hits Clinical Trials*, SINGULARITYHUB.COM (June 8, 2009), http://singularityhub.com/2009/06/08/proteus-ingestible-microchip-hits-clinical-trials/.

[35] *See Pills Get Smart*, *supra* note 1; Hirschler, *supra* note 12.

[36] *See* Royal Philips Electronics, *Philips' IntelliCap Targets Drug Development and Treatment for Digestive Tract Diseases* (Nov. 11, 2008), http://www.newscenter.philips.com/main/research/news/press/2008/081111-ipill.wpd.

[37] *See* Mark Lavender, *Regulating Innovative Medicine: Fitting Square Pegs in Round Holes,* 2005 DUKE L. & TECH. REV. 1, at 2.

B. *The Economics of Developing Smart Pills*

Smart pills not only provide therapeutic benefits over conventional drugs, but have several economical advantages. One study estimates that 13 percent of health care expenditures in the United States are due to patients failing to take medication as prescribed.[38] Using smart pills to track when patients take their medication may improve compliance and lower overall treatment costs.[39] Pharmaceutical manufacturers may also realize additional revenue by ensuring that patients do not skip doses, ensuring that prescriptions are consumed, and thus refilled, in a timely manner.[40] Additionally, pharmaceutical companies may be able to increase the revenue they generate from each prescription by charging more for smart pills compared to the stand-alone drug.[41]

Moreover, smart pills may provide new solutions to troubled drug firms. According to one industry expert, "[t]he paradigm of medicinal chemistry that pharmacology has been operating on for 40 to 50 years has been pretty well exhausted. . . . The low-hanging fruit has been picked."[42] This can be seen by the fact that the number of new drug approvals has declined while the cost of research and development continues to rise.[43] Many drug firms have failed to find solutions to replace the revenue from blockbuster drugs that have or soon will lose patent protection.[44] Additionally, they are facing intensified competition from generic drug manufacturers.[45] New smart pill products could fill gaps in the product pipelines of these drug companies. And selling ancillary services, such as monitoring and controlling drug intake by smart pills, may allow drug firms to diversify and stabilize their revenue.[46]

However, developing smart pills is by no means a cheap solution, nor do they address all of the economic problems facing drug companies. It costs pharmaceutical companies over $1 billon on average to bring each new drug to market.[47] And attempting to incorporate a medical device into a drug has the potential to drive up research and development costs even more. Consequently, it may only make sense for sponsors to develop smart pills in certain situations.

It is unlikely that a sponsor would combine a device with a new drug before the drug is first approved as a stand-alone therapy.[48] Sponsors will likely first try

---

[38] *See* NEW ENGLAND HEALTHCARE INSTITUTE, MEDICATION ADHERENCE AND CARE TEAMS 5 (2010), http://www.nehi.net/uploads/full_report/care_teams_paper__final__electronic.pdf; *see also Pills Get Smart*, *supra* note 1; *Smart Pill*, BURRILLREPORT.COM (Jan. 14, 2010), http://www.burrillreport.com/article-2065.html.

[39] *See* BURRILL & CO., *supra* note 1.

[40] *See Pills Get Smart*, *supra* note 1 (explaining that pharmaceutical companies "currently lose billions of dollars in sales from patients on long-term prescriptions who do not take their pills.").

[41] *Id.* (arguing that a pill is more valuable to insurers and national health systems because it has features that encourage patients to take the pill and ensure it is working well.); *see also* Hirschler, *supra* note 12.

[42] *See* Hepp, *supra* note 4.

[43] *See* BURRILL & CO., *supra* note 1.

[44] *Id.*

[45] *See* Deena Beasley & Ben Hirschler, *Ending Drug Companies' Addiction to Price Rises*, REUTERS, May 12, 2011, http://www.reuters.com/article/2011/05/12/us-summit-prices-idUSTRE74B4Z620110512.

[46] *Id.*

[47] *See* Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 477 (2007) (estimating that average R&D costs are now $1.32 billion per new molecule approved by FDA).

[48] *See infra* notes 142-43 and accompanying text.

combining devices with drugs that already have FDA marketing approval. Because medical devices can be used to control drug delivery, an already-approved drug that is combined with a drug delivery device can acquire new uses, such as by releasing at a specific location and time, thereby enhancing the safety or efficacy of the drug. Such a modified drug could probably be covered by a new patent. The drug-turned-smart-pill may also qualify for a new indication, which may qualify the drug for a new marketing exclusivity term.[49] Both solutions could help the sponsor thwart generic competition.

Another likely possibility is that a sponsor may combine an experimental drug with a device to "rescue" a drug in development that would otherwise fail to obtain FDA marketing approval. It takes an enormous amount of time and money to conduct full-scale clinical trials for new drugs, and even then success is far from guaranteed.[50] Fewer than 20 percent of drugs that begin human clinical trials are approved for marketing by FDA.[51] The remaining more than 80 percent usually fail to demonstrate adequate safety and efficacy in the general patient population.[52] Smart-pill technology could be used to convert one of these otherwise "unsafe" drugs into a "safe" drug by incorporating a medical device that would improve the efficacy of the drug or reduce adverse reactions to the drug, thereby ensuring that the drug is only administered in a safe and effective manner. For example, a drug candidate may be toxic or ineffective in acidic environments, such as the stomach, but may be safe and effective in non-acidic environments, such as the small intestines. This drug could be combined with a drug-delivery device that could control the release of the drug so that it is delivered only to the small intestines. In this way, the "unsafe" drug could be saved by converting it into a smart pill that uses a medical device to eliminate the adverse effects of the drug.

C. *The Regulatory Pathway for Smart Pills*

Smart pills have the potential to improve both the quality of patient care and the bottom line of the pharmaceutical industry. But neither of these improvements can be realized until the first smart pill receives marketing approval from FDA. Traditionally, drugs are regulated by the Center for Drug Evaluation and Research (CDER), while medical devices are regulated by the Center for Devices and Radiological Health (CDRH).[53] Smart pills, however, are combination products consisting of a drug and a device.[54] The agency typically attempts

[49] It is beyond the scope of this article to analyze potential marketing exclusivity related to smart pills.

[50] *See* PETER BARTON HUTT ET AL., FOOD AND DRUG LAW: CASES AND MATERIALS 776, 778 (3d ed. 2007). The average cost of an approved new drug is over $1 billion and the total drug development time is over 15 years now. *Id.* at 776, 778.

[51] TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT, IMPACT REPORT 2009: LARGE PHARMA SUCCESS RATE FOR DRUGS ENTERING CLINICAL TRIALS IN 1993-04: 16% (K.I. Kaitin ed., 2009); HUTT ET AL., *supra* note 50, at 630.

[52] Lawrence J. Lesko & Janet Woodcock, *Translation of Pharmacogenomics and Pharmacogenetics: A Regulatory Perspective*, 3 NATURE REV. DRUG DISCOVERY 763, 764 (2004); HUTT ET AL., *supra* note 50, at 624. In addition to safety and efficacy, a drug candidate might fail to make it to market because of commercialization issues. Lesko & Wookcock, *supra*.

[53] 21 C.F.R. § 3.2(b).

[54] Smart pills are combination products because they consist of a drug compoent and a device component. *See* definition of combination products.

to fit combination products into existing laws and regulations governing drugs and devices.[55] Generally, a combination product will be assigned to a lead center based on the product's "primary mode of action" and be subject to regulation by only that center.[56] The primary mode of action is the mode of action that is primarily responsible for the product's therapeutic effect—i.e., whether it primarily functions as a drug or a device.[57] Most drug-delivery systems (such as a pre-filled syringe or a drug-delivery patch) are reviewed by CDER because the most important therapeutic action of these products is attributable to the drug component, while the device component plays a secondary role.[58] Smart pills differ from conventional drug-delivery systems because the device component may have a crucial therapeutic action. Therefore, it is unclear whether smart pills will be regulated primarily as drugs or devices. Because there are substantial differences between CDER and CDRH, the agency's decision to assign a smart pill to one center or the other will determine what regulations the sponsor must comply with to receive marketing approval.[59] Furthermore, smart pill sponsors may have to comply with the regulations of both centers in certain situations.[60] Regardless of whether a smart pill is regulated as a drug or a device, it will be regulated by an FDA framework largely fashioned before combination products ever existed — a framework that is poorly designed to handle such products.

D. *The Challenges of Bringing Smart Pills to Consumers*

Despite the promising features of smart pills, few companies are developing smart-pill technology.[61] The development of smart pills is hindered by the uncertainty over how the current regulatory regime will be applied to smart pills. In fact, navigating FDA regulations is the most challenging issue faced by many innovative combination products.[62] Smart pills, like other combination products, have more than one "mode of action" and may be subject to more than one set of regulations.[63] Since most companies developing smart pill technology are device firms, they may be surprised when FDA forces them to satisfy the more difficult burden imposed by drug regulations—regulations that these firms have likely never seen before and which they are unprepared to handle.[64]

---

[55] *See* Lavender, *supra* note 37, at 5.

[56] 21 U.S.C. § 353(g); Kristina J. Lauritsen & Thinh X. Nguyen, *Combination Products Regulation at the FDA*, 85 CLINICAL PHARMACOLOGY & THERAPEUTICS 468, 469 (2009).

[57] 21 C.F.R. § 3.2(m).

[58] *See* FDA, *supra* note 17.

[59] *See* Lavender, *supra* note 37, at 3.

[60] *See* FDA, NUMBER OF MARKETING APPLICATIONS FOR A COMBINATION PRODUCT 2-3 (2005) (listing examples where two marketing applications might be necessary for a combination product), *available at* http://www.fda.gov/downloads/CombinationProducts/RequestsforComment/UCM108197.pdf.

[61] *See Pills Get Smart*, *supra* note 1 (mentioning two other firms in the competition of smart pills).

[62] *See* Susan Bartlett Foote & Robert J. Berlin, *Can Regulation be as Innovative as Science and Technology? The FDA's Regulation of Combination Products*, 6 MINN. J.L. SCI. & TECH. 619, 622, 631 (2005).

[63] *Id.* at 636.

[64] *See* Kevin Elder, Comment, *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*, 12 TUL. J. TECH. & INTELL. PROP. 221, 223 (2009).

II. FDA REGULATION OF DRUG/DEVICE COMBINATION PRODUCTS

Combination products are products that "constitute a combination of a drug, device, or biological product."[65] Drugs are basically chemical compounds that are intended for use in treating diseases,[66] while devices are instruments and machines that are intended for diagnosing or treating diseases but do not function primarily through chemical action or require metabolization.[67] In contrast, combination products, such as drug-eluting stents and pre-filled syringes, are neither pure drugs nor pure devices and therefore do not fit neatly into one of the three conventional categories of drug, device, or biologic.[68] To address the issues raised in developing and regulating these innovative combination products, FDA established the Office of Combination Products (OCP) in December 2002.[69] The OCP's primary responsibilities include assigning a combination product to a lead center, ensuring premarket review and postmarket regulation, and resolving inter-center disputes regarding premarket review.[70]

A. *Determining a Lead Center*

The OCP assigns a product to a particular center based on the product's "primary mode of action."[71] The primary mode of action is defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product."[72] If the primary mode of action of a combination product is that of a drug, then CDER has primary jurisdiction over the product. Similarly, if the primary mode of action is that of a device, then CDRH has primary jurisdiction.[73]

Typically, a sponsor of a combination product will submit a "Request for Designation" to the OCP asking the office to make its assignment decision before the sponsor submits a marketing application to FDA.[74] FDA procedures for inter-center

---

[65] 21 U.S.C. § 353(g). Combination products include:

> (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (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 . . . .

21 C.F.R. § 3.2(e).

[66] *See* 21 U.S.C. § 321(g)(1).

[67] *See id.* at § 321(h).

[68] *See supra* note 65.

[69] *See* Lauritsen & Nguyen, *supra* note 56.

[70] *Id.*

[71] *See* Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16, 104 Stat. 4511 (codified at 21 U.S.C. § 353(g)); 70 Fed. Reg. 49,848 (Aug. 25, 2005); Assignment of Agency Component for Review of Premarket Applications, 56 Fed. Reg. 58,754, 58,574 (Nov. 21 1991) (codified at 21 C.F.R. pt. 3).

[72] 21 C.F.R. § 3.2(k), (m). Mode of action is defined as "the means by which a product achieves its intended therapeutic effect or action."

[73] *See* Safe Medical Devices Act of 1990, *supra* note 71.

[74] 21 C.F.R. § 3.5(b). The OCP is supposed to make the jurisdictional determination within sixty days of receiving the Request for Designation. *See* FDA, RFD PROCESS, http://www.fda.gov/CombinationProducts/RFDProcess/default.htm.

consultative and collaborative review are supposed to ensure timely and effective inter-center communication and consistency in the review process.[75] However, assigning a combination product to a lead center can be complicated in two situations. The first situation is when the OCP cannot determine the primary mode of action. In this case, the OCP uses an assignment algorithm.[76] If there is a center that has regulated other combination products with similar safety and efficacy questions, the OCP will assign the combination product to that center.[77] Otherwise, the OCP will assign the combination product to the center with the most expertise related to the most significant safety and efficacy questions presented by the combination product.[78]

The second situation when assignment is complicated is when a sponsor seeks approval of two marketing applications.[79] FDA may require two marketing applications when the combination product has separate and complex components, such as when two products are sold individually but labeled specifically for use together (for example, a new drug that is indicated for use with an implantable delivery pump).[80] Alternatively, a sponsor may voluntarily submit two marketing applications to receive benefits that are available only through a particular type of application.[81] For example, where a device application is sufficient for a drug/device combination product, the sponsor may choose to submit a drug application if the drug qualifies as an orphan drug so that the product may receive benefits under the Orphan Drug Act.[82]

In order to market a new prescription drug or medical device, the pharmaceutical sponsor or the device manufacturer must first obtain regulatory approval from FDA.[83] However, drugs and devices are regulated in completely separate ways. Consequently, regardless of whether the OCP assigns a smart pill to CDER or CDRH, seeking regulatory approval for smart pills is complicated because a sponsor may have to comply with two sets of FDA regulations—those governing drugs and those governing devices.[84]

---

[75] *See* FDA, Intercenter Consultative/Collaborative Review Process (Sept. 9, 2010), http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm135860.htm.

[76] *See* Safe Medical Devices Act of 1990*, supra* note 71.

[77] *Id.*

[78] *Id.*

[79] *See* FDA, *supra* note 60.

[80] E-mail from the OCP to Author (June 29, 2011, 7:45 AM PST) (on file with author).

[81] *Id.* Some benefits of submitting two applications are new drug product exclusivity, orphan drug benefits, and proprietary data protection when two firms are involved.

[82] The Orphan Drug Act of 1983 encourages pharmaceutical companies to develop drugs targeting rare diseases. The Orphan Drug Act defines a rare disease as any disease that affects fewer than 200,000 individuals in the United States. The Act encourages sponsors to develop so-called "orphan drugs" by providing multiple incentives, including seven years of exclusive marketing rights, tax credits for certain clinical testing expenses, research grants, FDA user fee waivers, and occasionally expedited FDA review for market clearance or approval. FDA also often provides additional assistance to sponsors of orphan drugs in developing and executing clinical trials, helping to bring the orphan drug to market as quickly as possible. *See* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa-360ee); Marlene E. Haffner, *Orphan Products–Ten Years Later and Then Some*, 49 FOOD DRUG COSM. L.J. 593, 601 (1994) ("For the 70 drugs approved by the FDA in 1993, approval time averaged 33.1 months; the approval time for orphan drugs in that year averaged 12.8 months."); Avery, *supra* note 1, at 62.

[83] *See* 21 U.S.C. § 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug."); 21 U.S.C. § 360(e) (new medical devices developed after May 28, 1976 are subject to premarket approval).

[84] *See* FDA, GUIDANCE FOR INDUSTRY AND FDA STAFF: EARLY DEVELOPMENT CONSIDERATIONS FOR INNOVATIVE COMBINATION PRODUCTS 4 (2006), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126054.pdf.

B. *Regulation of Drugs*

If the drug component of a smart pill is new—that is, it has not already been approved as a stand-alone drug—FDA may regulate the smart pill as a new drug product. A new drug product cannot be marketed until FDA approves the drug as safe, effective, and properly labeled.[85] To obtain FDA marketing approval, the sponsoring pharmaceutical company must perform extensive testing and analysis on the new drug in order to demonstrate: (1) that the drug is safe and effective for the use according to the proposed labeling and (2) that the benefits of the drug outweigh its risks.[86] The new drug development process consists of three steps: preclinical research, human clinical studies, and new drug application review.[87] Once human clinical trials are complete, the sponsor may file a New Drug Application (NDA),[88] which requires the sponsor to provide detailed reports of all prior animal and human studies.[89] The sponsor must also include proposed labeling for the drug with the NDA, and FDA will reject the application if it finds the proposed labeling is in any way false or misleading.[90] FDA then reviews the application and, if the agency determines the drug is safe and effective, approves the NDA, allowing the sponsor to immediately begin marketing the drug.[91]

Alternatively, if the drug component of a smart pill is an existing drug that has already been approved by FDA, then the agency may regulate the drug component

---

[85] *See* 21 U.S.C. § 355 (b).

[86] *See* 21 C.F.R. § 312.23; FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, THE CDER HANDBOOK 7 (1998) [hereinafter FDA, THE CDER HANDBOOK], http://www.fda.gov/cder/handbook/handbook.pdf.

[87] FDA, THE CDER HANDBOOK, *supra* note 86, at 3. Before human clinical testing can begin on a drug candidate, the sponsor must complete substantial preclinical testing, which involves laboratory and animal tests. Next, the sponsor must precede through the investigational new drug (IND) process and conduct human clinical studies designed to demonstrate that the drug is safe and effective. *See* 21 U.S.C. § 355(d); 21 C.F.R. § 312.23. The IND process usually begins with Phase I clinical studies, which are generally conducted in twenty to eighty healthy subjects. *See* FDA, THE CDER HANDBOOK, *supra* note 86. These studies are designed primarily to evaluate the safety of the drug. *Id.* at 8. In Phase II clinical studies, the drug is generally tested on several hundred patients with the targeted disease. *Id.* Phase II studies are conducted to obtain preliminary data on the drug's effectiveness. *Id.*; *see also* 21 C.F.R. § 312.21(b). If the preliminary data from the Phase II trials suggests the drug is effective, the sponsor may proceed to Phase III trials. FDA, THE CDER HANDBOOK, *supra* note 86, at 8. The pivotal Phase III trials are conducted to gather sufficient information about the drug's safety and efficacy to extrapolate the results to the general population. *Id.*; *see also* 21 C.F.R. § 312.21(c). Phase III studies are the most important and expensive trials, generally involving several thousand patients with the targeted disease and costing hundreds of millions of dollars. *See* Gen Li, *Site Activation: The Key to More Efficient Clinical Trials*, PHARM. EXEC. (Dec. 12, 2008) (reporting that single clinical trial can involve up to 50,000 patients, last five years or longer, and cost up to $500 million); THE CDER HANDBOOK, *supra* note 86, at 9.

[88] This article refers to NDAs. Developers of biological products file Biologicals License Applications (BLAs) rather than NDAs. For purposes of this article, any discussion of NDAs is also applicable to BLAs.

[89] *See* Pennington Parker Landen, *Federal Preemption and the Drug Industry: Can Courts Co-Regulate?*, 43 FOOD DRUG COSM. L.J. 85, 100 (1988); *see also* 21 U.S.C. § 355(a)-(b). In general, the NDA should contain reports on the following: (1) chemistry, manufacturing, and control; (2) nonclinical pharmacology and toxicology; (3) human pharmacokinetics and bioavailability; (4) clinical efficacy and safety data (both generally and by gender, age, and race). *See* 21 C.F.R. § 314.50; *see also* FDA, THE CDER HANDBOOK, *supra* note 86, at 21.

[90] 21 U.S.C. § 355(b)(1)(F), (d)(7). All drugs must include labeling, which is printed material accompanying the drug that describes, among other things, information concerning dosages, directions for administration, conditions for which the drug is effective, contraindications, and warnings about known or suspected side effects and adverse reactions. *See* 21 U.S.C. §§ 321(m), 352(f)(1)-(2).

[91] *See* 21 U.S.C. § 355(d); *id.* § 355(a).

as a generic drug.[92] Instead of filing a full NDA, a generic drug manufacturer merely needs to file an abbreviated new drug application (abbreviated NDA or ANDA), which only requires the applicant to show that its generic drug has the same active ingredient, the same basic pharmacokinetics, and is bioequivalent to the brand-name drug.[93] But a generic applicant is not required to provide independent proof of safety and efficacy, and can instead rely on the NDA holder's clinical trial data.[94] However, if the drug component of a smart pill is a related to, but materially different from an approved drug (e.g., in dose, route of administration, or active ingredient), the sponsor cannot directly submit an ANDA.[95] Instead, the sponsor can submit a "suitability petition" to FDA that argues that additional studies showing safety and effectiveness are not needed.[96] If the agency grants the petition, the sponsor may submit an ANDA.[97] Otherwise, the sponsor must file either a full NDA or a so-called section 505(b)(2) NDA.[98] A section 505(b)(2) NDA allows the sponsor to use published literature and FDA's prior safety and efficacy determinations.[99] Therefore, the sponsor only needs to show the safety and effectiveness of the *differences* between the pioneer drug and the modified drug.[100]

C. *Regulation of Medical Devices*

FDA may regulate the device component of a smart pill as a medical device. Depending on the safety risks posed by a device, FDA classifies devices as Class I, II or III, with increasing levels of regulatory control for each class.[101]

Class I devices present minimal safety risks and are generally exempt from premarket review and subject only to minimal "general controls."[102] Class II devices pres-

---

[92] According to FDA, "[a] generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price." FDA, Office of Generic Drugs Home Page, http://www.fda.gov/cder/ogd/ (last visited Nov. 13, 2008). A generic drug is bioequivalent to a listed drug if—

> (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.

21 U.S.C. § 355(j)(8)(B).

[93] *Id.*; 21 U.S.C. § 355(j)(2)(A)(ii)–(iv).

[94] 21 U.S.C. § 355(j)(2)(A). The ANDA process ensures the quality of generic drugs, simplifies the generic approval process, eliminates duplicative research costs associated with clinical trials, and accelerates consumer access to affordable drugs. *See* Requirements for Submission of In Vivo Bioequivalence Data, 68 Fed. Reg. 61,640, 61,645 (proposed Oct. 29, 2003) (to be codified at 21 C.F.R. pts. 314 & 320) (reporting estimates of ANDA preparation and filing costs between $300,000 and $1 million); Thomas Chen, Note, *Authorized Generics: A Prescription for Hatch-Waxman Reform*, 93 VA. L. REV. 459, 464 (2007). Upon ANDA approval, the generic manufacturer may begin commercially marketing its generic equivalent. 21 U.S.C. § 355(j)(2)(A).

[95] *See* HUTT ET AL., *supra* note 50, at 760.

[96] *Id.*

[97] *Id.*

[98] *Id.*

[99] 21 U.S.C. § 355(b)(2); HUTT, *supra* note 50, at 770.

[100] HUTT, *supra* note 50, at 770. A section 505(b)(2) NDA applicant can rely on published studies to demonstrate safety and effectiveness of approved drug products and therefore saves time and expense for sponsors. *Id.* A section 505(b)(2) NDA application should include: identification of the portions of the application that rely on information not from the applicant; information related to market exclusivity; a bioavailability/bioequivalence study; information with respect to any patents; and studies necessary to support the change or modification from the listed drug or drugs. *Id.*

[101] *See* 21 U.S.C. § 360c(a)(1).

[102] General controls require the manufacturer to register the device with FDA, manufacture it in accordance with Good Manufacturing Practices, and provide proper labeling for the device. *See* FDA, Device Classes, http://www.fda.gov/CDRH/DEVADVICE/3132.html; 21 U.S.C. §§ 351, 352, 360, 360f, 360h, 360i, 360j; *see also* 21 C.F.R. §§ 801, 809, 820.

ent moderate risk and typically require submission of a so-called 510(k) premarket notification,[103] which requires the sponsor to show that the device is "substantially equivalent" to an approved predicate device.[104] Class III devices are those that may present serious safety risks to the patient.[105] Sponsors of Class III devices must submit a premarket approval (PMA) application that includes data showing that the device is safe and effective for its intended use.[106] However, unlike the NDA process for new drugs, a premarket approval application does not necessarily require clinical trial data.[107] Consequently, the premarket approval process, which is the most rigorous regulatory process for devices, is often substantially less rigorous, and therefore less expensive, than the NDA process for drugs. The premarket approval application must be approved by FDA before the sponsor can commercially market the device.[108] After a device has been classified into one of the three classes, the sponsor must develop the information necessary to obtain FDA clearance to market.[109] Although the agency requires clinical data for some 510(k) submissions and most premarket approval applications,[110] the amount of data required is typically less than what CDER demands for a NDA.

This article assumes that smart pills contain a device component that is ingested with the drug. Consequently, it is useful to review how FDA has regulated ingestible medical devices. One example of an ingestible medical device is an ingestible telemetric gastrointestinal capsule imaging system, which is also known as a "PillCam." A PillCam is typically a small camera or other imaging device encased in a capsule.[111] A patient can swallow the PillCam, which will then move through the patient's gastrointestinal tract and record images. These images can be stored in the device or wirelessly transmitted to a recording device.[112] An

---

[103] Note that general controls require submission of a 510(k) premarket notification for both Class I and II devices. *See* 21 U.S.C. §§ 360(k), 360c(i). However, by regulation, almost all Class I and many Class II devices are exempt from the 510(k) submission requirement. *See* 21 C.F.R. §§ 862-892; FDA, CLASS I/II EXEMPTIONS, http://www.fda.gov/CDRH/DEVADVICE/3133.html.

[104] *See* 21 U.S.C. §§ 360(k), 360c(i). A predicate device is basically any device that has already been approved by FDA. *See* FDA, PREMARKET NOTIFICATION 510(K), http://www.fda.gov/CDRH/DEVADVICE/314.html. In addition to general controls, FDA can subject Class II devices to "special controls," which may include special labeling requirements, mandatory performance standards, and post-market surveillance. *See* 21 U.S.C. § 360c(a)(1)(B).

[105] *See id.* § 360c(a)(1)(C)(ii). Note that devices with no equivalent predicate are classified as Class III devices by default, regardless of their safety. Consequently, sponsors of these devices can use a so-called *de novo* option to request a down-classification to either a Class I or II device if they can show the device presents only a low or moderate risk. *Id.* If FDA approves the down-classification, the device can be marketed without obtaining a premarket approval application. *See* FDA, CENTER FOR DEVICES & RADIOLOGICAL HEALTH, NEW SECTION 513(F)(2) – EVALUATION OF AUTOMATIC CLASS III DESIGNATION, GUIDANCE FOR INDUSTRY AND CDRH STAFF (1998).

[106] *See* 21 U.S.C. § 360c(a)(1)(C).

[107] *See* HUTT ET AL., *supra* note 50, at 1010-12.

[108] *See* 21 U.S.C. § 360e.

[109] *See* FDA, HOW TO MARKET YOUR DEVICE (2010), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/default.htm. Before FDA issues marketing clearance, the sponsor must assure that the device is properly labeled. *Id.* If a medical device is intended for use with a specific branded drug, FDA requires that the drug and device have mutually conforming labels. FDA, *supra* note 58, at VII.A.1(a)ii., VII.B. After FDA issues marketing clearance, the sponsor must register and list the device with the agency. *See* FDA, *supra* note 105.

[110] FDA. *supra* note 105, at 2. In these cases, sponsors must conduct trials in accordance with FDA's Investigational Device Exemption regulation. *Id.*

[111] This type of device includes an ingestible capsule, with imaging capturing ability, and data transfer, storage, and process parts. *See* 21 C.F.R. § 876.1300.

[112] The device may also transmit gastrointestinal motility data to a wireless receiver worn by the patient. *See id.*

external system can also calculate the position of the PillCam in the patient's body based on the strength of the wireless signal emitted by the device.[113] FDA originally regulated PillCams as Class III devices. Then in 2001, FDA reclassified ingestible telemetric gastrointestinal capsule imaging systems as Class II devices with special controls.[114] The special controls include special labeling instructions, biocompatibility testing, and software testing, which are designed to assure the safety and efficacy of the PillCam.[115]

D. *Example Combination Product: The Drug-Eluting Stent*

One example of a drug-device combination product is a drug-eluting stent. A stent is a tiny metal scaffold that can be placed into an artery (or vein) that has become clogged to prop it open. The newest generation of stents is coated with drugs that retard cell growth and prevent restenosis, which is when the patient's cells grow around the stent to re-clog the artery.[116] These so-called drug-eluting stents were the first major combination product approved by FDA.[117] The OCP assigns drug-eluting stents to CDRH for review and considers their primary mode of action to be that of a device.[118] CDRH classifies drug-eluting stents as Class III devices and requires an investigational device exemption and premarket approval application.[119]

Although the OCP had determined that the primary mode of action of drug-eluting stents was that of devices, the drugs coated on these stents and the polymers used to load the drugs significantly affected their safety and efficacy.[120] Therefore, drug-eluting stents were subject to many requirements from both CDRH and CDER.[121] Dual regulations, lack of collaborative efforts between centers, and limited resources within each center all led to considerable delay of marketing approval.[122]

---

[113] The capsule passes naturally from the body with the stool, where it can be recovered. *See* Reena Sidhu et al., *Gastrointestinal Capsule Endoscopy: From Tertiary Centres to Primary Care*, 332 BRITISH MED. J. 528, 528 (2006), *available at* http://www.bmj.com/content/332/7540/528.full.

[114] *See* FDA, CLASS II SPECIAL CONTROLS GUIDANCE DOCUMENT: INGESTIBLE TELEMETRIC GASTROINTESTINAL CAPSULE IMAGING SYSTEM; FINAL GUIDANCE FOR INDUSTRY AND FDA (2001), *available at* http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm073393.htm; *see also* 21 C.F.R. § 876.1300. Regarding special controls, see note 104, *supra*.

[115] *See* FDA, *supra* note 114 (identifying six types of risks associated with this type of device).

[116] Drug-eluting stents have proven to be far superior to bare-metal stents. The first drug-eluting stent reduced restenosis rates from over 25% to 7.9%. *See News from the Transcatheter Cardiovascular Therapeutics Meeting*, CATH LAB DIG. (Oct. 1, 2003), http://www.cathlabdigest.com/article/2181.

[117] *See* FDA, *Examples of Combination Product Approvals*, http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101598.htm.

[118] *See* FDA, NEWS RELEASE: FDA APPROVES DRUG-ELUTING STENT FOR CLOGGED HEART ARTERIES (2008), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116848.htm.

[119] FDA Medical Device database search on coronary drug-eluting stents showed all the stents were approved based on a PMA. *See* FDA, GUIDANCE FOR INDUSTRY CORONARY DRUG-ELUTING STENTS — NONCLINICAL AND CLINICAL STUDIES COMPANION DOCUMENT (2008), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072196.pdf. An investigational device exemption allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a premarket approval application or a premarket notification submission to FDA. *See* FDA, Device Advice: Investigational Device Exemption (IDE) (last updated April 26, 2009), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm.

[120] *See* 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.

[121] *Id.*

[122] *See* Edler, *supra* note 64, at 225.

The first drug-eluting stent received FDA marketing approval in 2003.[123] However, it took another four years for the agency to grant market clearance to second-generation drug-eluting stents,[124] despite the fact that the only difference between the two generations was a relatively minor change in the design of the stents.[125] The manufacturers expected less severe regulations for the second-generation drug-eluting stents, but FDA maintained surprisingly stringent requirements for approval of the second-generation products.[126] FDA still classifies drug-eluting stents as Class III devices notwithstanding the fact that predicate devices are now on the market that could be used to support a Class II classification. The agency probably maintained this heightened regulation for one of two reasons. First, the Vioxx recall in 2004 raised concerns about FDA's approval process and the agency was wary of making another mistake while under severe political and public scrutiny.[127] Second, FDA may have had legitimate concerns that the design changes in the second-generation drug-eluting stents would cause adverse effects.[128]

The history of FDA's regulation of drug-eluting stents is very instructive to sponsors of smart pills and other drug/device combination products. Drug-eluting stents were the first major combination products approved by FDA and became a multi-billion dollar market within five years of FDA approval despite the difficulties faced by both FDA and the industry.[129] The drug-eluting stent manufacturers, all of which were medical device companies, were unfamiliar with and unprepared for CDER requirements.[130] They should have understood that stents coated with drugs would bear more scrutiny than bare-metal stents.[131] Therefore, they should have anticipated meeting both CDER and CDRH requirements and provided enough information to avoid delays in approval.[132] However, FDA could have helped sponsors by providing specific instructions to guide them through the review process.[133] In response, FDA issued a detailed draft guidance document in 2008 detailing how it will regulate coronary drug-eluting stents.[134] Since then, the number of approved drug-eluting stents has significantly increased.[135]

---

[123] *Id.*

[124] *Id.* at 228-29.

[125] *See* Richard A. Lange & David Hillis, *Second-Generation Drug-Eluting Coronary Stents*, 362 NEW ENG. J. MED. 18 (2010). The newer stents used a flexible cobalt-chromium stent frame with thin struts while the older stents used a less flexible stainless steel stent with thicker struts. *Id.*

[126] *Id.*; *see also* FDA, *supra* note 119. A product classification search on the FDA website (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm) showed that all approved DESs were Class III devices and required premarket approval application.

[127] In 2004, Merck voluntarily recalled its blockbuster drug Vioxx because of an increased risk of cardiovascular complications for patients who had taken the drug for an extended period of time. *See* Elder, *supra* note 64, at 228. And in 2005, a multiple sclerosis drug approved by FDA's accelerated approval program was pulled of the market after a patient died. *See* Ricardo Alonso-Zaldivar & Denise Gellene, *Warning Didn't Slow Approval of MS Drug*, L.A. TIMES, Mar. 2, 2005, http://articles.latimes.com/2005/mar/02/business/fi-biogen2.

[128] *See* Elder, *supra* note 64, at 229-30.

[129] *See* Alla Katsnelson, *Biotech's Hidden Stepsister*, SCIENTIST, Oct 2008, at 33, 35.

[130] *See* Elder, *supra* note 64.

[131] *Id.*

[132] *Id.*

[133] *Id.*

[134] *See* FDA, *supra* note 119. The goal of the guidance was to reduce the review time for drug-eluting stents and to help stent manufacturers prepare the premarket approval application. *Id.*

[135] FDA, PMA – Premarket Approval Database [hereinafter PMA Database], http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. The Authors searched the PMA Database over four major drug-eluting stents: Xience by Abbott, Taxus by Boston Scientific, Cypher by Cordis, and Endeavor by Medtronic. The total numbers of annualy approved PMAs from 2003 to 2010 are 3, 11, 19, 24, 25, 58, 88, and 82, respectively.

III. FDA REGULATION OF SMART PILLS

As discussed previously, FDA will likely regulate smart pills as ingestible drug/device combination products. Based on the agency's determination of a primary mode of action, the Office of Combination Products will assign the potential therapy to either CDER or CDRH for premarket review. No matter which center is designated as the lead center, it is important and beneficial for smart pill sponsors to understand the requirements of both centers for multiple reasons. First, regardless of the designation, certain regulations from both CDER and CDRH may apply.[136] Second, the OCP's designation decisions are inconsistent and unpredictable, such that similar products can be assigned to different lead centers.[137] Third, a sponsor may seek marketing approval from both CDER and CDRH, either because FDA requires dual-approval or because dual-approval is strategically beneficial to the sponsor.[138] For example, even though a smart pill may only require CDRH approval, a sponsor may want to submit an NDA in order to quality for orphan drug benefits or other forms of marketing exclusivity.[139] Therefore, understanding the requirements of both CDER and CDRH can enable sponsors of smart pills to determine the best premarket application strategy and to prepare for what may be unfamiliar and unexpected regulations.

At the time of this writing, we know of no smart pill products that have received marketing approval from FDA or have even sought such approval.[140] Thus, it is unclear how FDA will regulate smart pills. But it is possible to predict the process the agency will use based on the current regulatory scheme. This analysis assumes that a smart pill comprises a drug component and a device component, and each of these components may have independent marketing approval. In other words, the drug component may be an "old drug" (i.e., covered by a NDA) or a "new drug" (i.e., not covered by a NDA). Similarly, the device component may be an "old device" (i.e., approved by CDRH) or a "new device" (i.e., not approved by CDRH). Therefore, there are four possible regulatory combinations of smart pills: old drug/old device, old drug/new device, new drug/old device, and new drug/new device.[141] Whether the drug and device components are old or new will determine how the smart pill is regulated. Consequently, analysis of the regulatory requirements for each of the four combinations is needed to predict how FDA might regulate smart pills and to show why the current regulatory regime is inadequate.

Although there are four possible combinations in theory, some combinations are more likely than others in practice. To our knowledge, no ingestible medical devices

---

[136] *See* FDA, *supra* note 109.

[137] *See* Lavender, *supra* note 37. Kurt R. Karst & Jeffrey K. Shapiro, *FDA is Sued Over Product Designation Determination; Lawsuit Seeks Device Declaration and to Vacate FDA's Drug Findings*, FDA LAW BLOG, June 30, 2011, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2011/06/fda-is-sued-over-product-designation-determination-lawsuit-seeks-device-declaration-and-to-vacate-fd.html (reporting that a French company filed a complaint challenging FDA's determination that its canister-contained spray-on chemical burn treatment was a drug rather than a device).

[138] *See* FDA, *supra* note 79.

[139] *Id.*

[140] However, because marketing applications are confidential, it is possible that an application may have been filed and not yet made public.

[141] Interview with Marsha Cohen, Professor of Law, University of California, Hastings College of the Law (Sept. 20, 2010). While the authors recognize that the terms "old" and "new" may be misnomers with respect to certain drugs and devices, and that more accurate terms would be "approved" and "unapproved," respectively. However, for the sake of convenience and brevity, we choose to use the former terms. Note that the term "old drug" does not mean drug products that were grandfathered in under the FDCA.

that carry drugs have been approved by FDA.[142] Therefore a sponsor is currently unlikely to encounter either scenario involving an old device. In addition, it is unlikely that a sponsor would use a new drug in a combination product before the drug receives marketing approval as a stand-alone product.[143] If a sponsor tests a new drug as part of a smart pill combination product, the sponsor may have to perform another expensive and time-consuming clinical trial if the sponsor later wants to market the drug alone or in combination with another device. Absent some compelling reason, a sponsor is unlikely to pursue such a limiting regulatory pathway.[144] Consequently, a sponsor is also unlikely to encounter either scenario involving new drugs.[145] Therefore, the old drug/new device combination is currently the most likely scenario for the regulation of smart pills. However, the other scenarios may become more likely in the future as smart pills begin to enter the market. For example, once a smart pill has been approved for use with any drug, it becomes an old medical device.

A. *Old Drug, New Medical Device*

If a smart pill consists of an old drug and a new medical device, the OCP will most likely assign the product to CDER, notwithstanding the fact that the drug component is already covered by an NDA. This is because the designation is based on the "primary mode of action" principle, not the relative novelty of each component.[146] For example, a drug-eluting stent is primarily a stent, and the drug component plays a supplementary role. Accordingly, the OCP decided that the primary mode of action of a drug-eluting stent is that of a device and assigned CDRH as the lead center. The smart pills that are currently in development are primarily drugs that include some type of device for enhancing the delivery of the pills. Hence, the OCP would likely determine that the primary mode of action of a smart pill is that of a drug and assign the product to CDER.[147] However, it is possible for CDRH to be the lead center if the device component of a smart pill has some significant therapeutic functions.[148] Regardless of the OCP's assignment, smart pills, like drug-eluting stents, may nevertheless be subject to both CDER and CDRH authorities.[149]

If the OCP determines the primary mode of action of a smart pill is that of a drug, then the smart pill will follow the regulatory procedures of CDER. Since this scenario assumes the drug component is already approved by FDA, the sponsor

[142] FDA, 510(k) Premarket Notification database (hereinafter 510(k) Database), http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm; E-mail from the OCP to author (Jan. 7, 2011 1:26 PM PST) (on file with author). The authors searched the PMA Database and the 510(k) Database for "Proteus Biomedical" and "Philips," however this search yielded no relevant products. It is possible that an ingestible drug/device combination product has been approved by FDA through CDER but not through CDRH. It is difficult to search the drug database without any drug name or company name.

[143] However, as discussed in Part I.B, *supra*, a sponsor may combine a new drug with a device in order to "rescue" the drug if it would otherwise fail to obtain FDA marketing approval.

[144] *See infra* Part III.C.

[145] In FY 2007 and FY 2008, no NDAs were filed for "device coated/impregnated/otherwise combined with drug" (combination product category 4), and the numbers of orginal INDs out of total applications were 7/103, 9/106, respectively. *See* FDA, *supra* note 14, at 24, A-1.

[146] *See supra* Part II.A.

[147] *See* FDA, *supra* note 58, at VII.A.1(b) (stating that for "Device with primary purpose of delivering or aiding in the delivery of a drug and distributed containing a drug," the Market Approval Authority is "CDER using drug authorities and device authorities, as necessary.").

[148] Since both the drug and the device components of smart pills can have therapeutic functions, it will be a case-by-case analysis and sometimes inconsistent designation. *See* general discussion in Part II.A, *supra*.

[149] *See supra note* 148.

will probably not be required to submit a full NDA. Instead, the sponsor could submit a suitability petition to FDA.[150] However it is unlikely that FDA will grant a suitability petition since it would be difficult for a sponsor to argue that a drug/device combination product is bioequivalent to a drug alone. Consequently, the sponsor will most likely have to submit a section 505(b)(2) NDA and show the safety and effectiveness of the difference between the existing drug and the drug/device combination product.

Novartis recently announced its plan to seek regulatory approval of the first smart pill.[151] Novartis will initially use one of its established drugs with Proteus Biomedical's Raisin microchips.[152] The Raisin microchip, an ingestible medical device, has not received any marketing approval from FDA.[153] Thus, the first potential smart pill will be a combination product consisting of an old drug and a new medical device. Novartis expects to conduct bioequivalence tests rather than a full-scale clinical trial because the microchips are added to an existing drug.[154]

However, FDA may subject Novartis's pioneering smart pill to additional regulations. FDA's Intercenter Agreement between CDER and CDRH specifically provides that CDER has the authority to approve drug-delivery devices for marketing, but the agreement also specifies that device regulations apply when necessary.[155] Therefore, even though CDER will be the lead center, the marketing approval of the smart pills may involve CDRH regulations and authorities.

As discussed previously, FDA classifies medical devices into three categories based on the safety risks posed by the device.[156] Based on FDA's regulation of ingestible medical devices, the agency will likely measure the safety of a smart pill based on the product's biocompatibility, electrical and mechanical safety, electromagnetic compatibility, functional reliability, and the risk of intestinal obstruction or injury.[157] FDA had initially categorized ingestible medical devices as Class III devices and required clinical data to establish safety and effectiveness. Even though FDA reclassified ingestible medical devices as Class II devices, FDA still requires some special controls, including biocompatibility testing for some ingestible medical devices.[158] In Novartis' smart pill, the Raisin microchip will be considered an ingestible medical device. The device has not yet received marketing approval from FDA. In fact, the Raisin microchip is such novel technology that it may be difficult for Novartis to show

---

[150] *See supra* Part II.B.

[151] *See* Hirschler, *supra* note 12.

[152] *Id.*

[153] Based on a search by the authors of the PMA Database and 510(k) Database, *supra* notes 135 and 142, respectively.

[154] *See* Hirschler, *supra* note 12.

[155] *See* FDA, *supra* note 58.

[156] *See supra* Part II.A.

[157] FDA listed six types of risks associated with ingestible telemetric gastrointestinal capsule imaging systems: (1) Biocompatibility; (2) Electrical and mechanical safety; (3) Radio-frequency radiated power and electromagnetic compatibility, including interference with other medical devices and with this device (e.g., interference with image acquisition); (4) Functional reliability, including structural integrity and image acquisition; (5) Intestinal obstruction or injury; and (6) Misinterpretation of the captured images. *See* FDA, CLASS II SPECIAL CONTROLS GUIDANCE DOCUMENT: INGESTIBLE TELEMETRIC GASTROINTESTINAL CAPSULE IMAGING SYSTEM; FINAL GUIDANCE FOR INDUSTRY AND FDA (2001), *available at* http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm073393.htm. Because the working mechanisms of the device component of a smart pill are similar to an ingestible gastrointestinal capsule, it is reasonable to assume that the safety measures of smart pills will be similar to those of the ingestible gastrointestinal capsules.

[158] For exampe, ingestible telemetric gastrointestinal capsule imaging systems (PillCams) and gatointestinal motility mointoring systems are Class II devices, although the PillCam was originally a Class III device.

that the microchip is substantially equivalent to a predicate device. Therefore, FDA will likely categorize the Raisin microchip as a Class III device, at least initially.[159] Accordingly, Novartis will likely have to submit a premarket approval application and perform clinical trials to obtain marketing approval from CDRH. Novartis may request down-classification to either a Class I or II device if they can show the device presents only a low or moderate risk.[160] However, because the technology is so novel, it is likely that FDA will maintain a Class III designation.

Furthermore, FDA might be more cautious with a new type of product, especially a product with the potential to transform the pharmaceutical industry and draw media attention.[161] The agency has conflicting mandates of helping to bring new medical treatments to the market while also keeping drugs and devices that are not proven to be safe and effective off the market.[162] However, the agency is extremely wary of adverse-event risks associated with new products, and especially new types and classes of treatments.[163] As discussed previously, FDA imposed heightened regulatory requirement on drug-eluting stents when they first sought marketing approval. Similarly, smart pills may face increased scrutiny from the agency because of their novelty. This attitude towards innovative treatments adds further uncertainty to the regulations the agency will impose on smart pills. If FDA regulates smart pills like it regulated drug-eluting stents,[164] then it is likely that FDA will require smart pill sponsor to meet relatively stringent requirements. This means that future generations of smart pills may continue to be regulated as Class III devices.[165]

To summarize, although FDA is unlikely to require NDA-type full-scale clinical trials for a smart pill consisting of an old drug and a new device, it is likely that more than bioequivalence tests will be needed to obtain FDA marketing approval. FDA publications suggest that additional authorities may be required for such combination products. Further, FDA could be more cautious when approving the new technology embedded in smart pills and subject the products to stricter regulations. Thus, in addition to the minimum bioequivalence tests, the sponsors of smart pills should be prepared to provide clinical data that satisfy Class III device requirement.

B. *Old Drug, Old Medical Device*

As discussed above, the OCP will most likely determine that the primary mode of action of a smart pill is that of a drug and assign the smart pill to CDER.[166] If this is the case, the sponsor will have two options. The first option would be to have FDA approve a suitability petition so the sponsor can file an ANDA, where it will only have to show bioavailability and bioequivalence data. However, if the agency rejects the suitability petition, the sponsor will have to submit a section 505(b)(2)

[159] Interview with Peter Barton Hutt, Senior Counsel, Covington & Burling LLP, in Wash., D.C. (Oct. 11, 2010).

[160] *See supra* note 105.

[161] *See Pills Get Smart*, *supra* note 1; Hirschler, *supra* note 12.

[162] *See FDA's Role in Identifying and Communicating Drug Safety Issues, statement before the House Committee on Veterans' Affairs*, July 9, 2008 (statement of Paul Seligman, Associate Director of Safety Policy and Communication, CDER), http://www.fda.gov/NewsEvents/Testimony/ucm096411.htm.

[163] *See Alzheimer's Disease: FDA's Role In New Product Development, Statement Before the Subcommittee on Retirement Security and Aging, Senate Committee on Health, Education, Labor and Pensions*, July 17, 2007 (statement of Andrew C. von Eschenbach, Commissioner of Food and Drugs, FDA), http://www.fda.gov/NewsEvents/Testimony/ucm110879.htm. FDA regulation of medical products is considered as the gold standard worldwide. Only about ten percent of the products in Phase 1 clinical testing receive marketing approval and half of the products that enter Phase 3 are never approved.

[164] *See supra* Part II.D.

[165] *See supra* notes 126-27 and accompanying text.

[166] *See supra* Part III.A.

NDA to show the safety and effectiveness of the difference between the existing drug with and without the device component.

Alternatively, if the OCP determines the primary mode of action of a smart pill is that of a device, then the smart pill will be assigned to CDRH. Depending on the smart pill's potential risks, the sponsor will need to submit either a 510(k) premarket notification or a PMA application.[167] Because the smart pill in this scenario involves an old medical device, the sponsor may be able to submit the less burdensome 510(k) notification, which only requires the sponsor to show that the smart pill is substantially equivalent to a predicate device. However, an old device combined with an old drug is substantially different from an old device standing alone. Consequently, unless the predicate device was also an ingestible drug/device combination product, CDRH will likely reject a sponsor's argument that the smart pill is substantially equivalent to an approved device. Therefore, like drug-eluting stents, it is most likely that the sponsor of a smart pill will have to submit a premarket approval application. This means that the sponsor gains little regulatory benefit by incorporating an old device rather than a new device into a smart pill. In both situations, the sponsor will likely have to perform expensive, time-consuming clinical trials to establish safety and efficacy.

Drug-eluting stents are examples of combination products consisting of an old drug and an old medical device. So far, the OCP has determined that the primary mode of action for every drug-eluting stent is that of a device and therefore assigned the combination products to CDRH.[168] Even though several drug-eluting stents are already on the market, new drug-eluting stents are still classified as Class III devices and require approval of a premarket approval application.[169] This suggests that FDA may reject any 510(k) premarket notification from a smart pill sponsor and require a premarket approval application. Even if the sponsor can point to a predicate device that is an ingestible drug/device combination product, CDRH may still regulate the smart pill as a Class III, as it has with drug-eluting stents.[170] Consequently, sponsors of next-generation of smart pills may be forced to continue submitting PMA applications in order to receive FDA marketing approval.

Regardless of the designation result, smart pills, like the drug-eluting stents, may be subject to both CDER and CDRH authorities.[171] Accordingly, smart pill sponsors should anticipate having to show that adding a device component to the existing drug neither adversely affects the safety and efficacy of the existing drug nor poses an increased risk compared to the device alone.

C. *New Drug, Old Medical Device*

If a smart pill consists of a new drug and an old medical device, it will likely be assigned to CDER because the primary mode of action is that of a drug. Because new drugs are subjected to higher regulatory standards than old devices, the safety and efficacy issues presented by the drug component of a smart pill will predominate. CDER has the best resources and expertise to address these issues.

---

[167] *See supra* Part II.C.

[168] *See supra* Part II.D.

[169] FDA Medical Devices database search.

[170] *See supra* Part II.D. New drug-eluting stents are still classified as Class III devices notwithstanding the fact that they are arguably substantially equivalent to previously approved drug-elution stents.

[171] *Id.* Also, regardless of which center is assigned regulatory responsibility for a particular smart pill, the sponsor will probably need to submit a petition to CDER for new labeling since the labeling of the smart pill will be different from the labeling of either component.

A new drug could be either a new molecular entity or an existing drug with a new use.[172] The smart pill manufacturer will have to proceed through the new drug application process to demonstrate the safety and effectiveness of the new drug. In short, the process requires preclinical research, clinical trials, and NDA review.[173]

Since the device component will be tested along with the drug component in clinical trials, it is unlikely that the sponsor will need to submit a separate device application to CDRH. The clinical data generated for the NDA should satisfy any data required by CDRH to show the safety and effectiveness of the product. The sponsor, however, may elect to submit two applications to qualify for marketing exclusivity or other benefits.[174]

D. *New Drug, New Medical Device*

Like the new drug/old device scenario, if a smart pill consists of a new drug and a new medical device, it will likely be assigned to CDER based on the primary mode of action principle. Because the NDA process for drug approval is generally more rigorous than any CDRH regulations, it is likely that only CDER approval would be necessary in this scenario. However, as discussed previously, a sponsor may elect to submit two applications to receive certain benefits.[175]

The new drug/new device scenario is most likely where the combination could create a new use for an existing drug or could "rescue" a drug that would otherwise fail clinical trials.[176] For example, if a drug is effective only with a customized dose, an embedded drug-delivery device could allow a physician to closely monitor the drug release and determine the best dose for a particular patient. Therefore, delivering the drug together with the device could convert an unsafe or ineffective drug into a product that satisfies FDA's safety and efficacy requirements.

IV. SUGGESTIONS FOR REGULATING SMART PILLS

Inconsistent designations and unclear regulations are among the biggest challenges for smart pill manufacturers trying to get FDA marketing approval. CDER and CDRH differ significantly on their safety and effectiveness requirements. For example, to demonstrate efficacy, CDER typically requires double-blinded placebo-controlled studies, while CDRH accepts other data and is therefore more flexible.[177] Other differences, including approval time, application fees, and product liability, also make CDRH a preferred center over CDER for many combination products.[178] Although some argue that CDRH is beginning to regulate devices in ways similar to the way CDER regulates drugs, it is generally cheaper and faster to

---

[172] FDA, THE CDER HANDBOOK, *supra* note 86, at 22.

[173] *See supra* Part II.B. Note that a 505(b)(2) NDA may not be sufficient in this scenario because a new use might bring with changes in dosage, dosage form, or methods of administration, which may raise questions about the safety of the drug under those changed circumstances. Interview with Marsha Cohen, Professor of Law, University of California, Hastings College of the Law (July 11, 2011); *see also* FDA, GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(B)(2), at 4 (1999), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf.

[174] *See supra* Part II.C.

[175] *See supra* Part II.C.

[176] *See supra* Parts I.B, III.C.

[177] *See* Lavender, *supra* note 37.

[178] *Id.*

get approval through CDRH than through CDER.[179] Notwithstanding CDRH's less burdensome regulation, CDER review of a new product may be desirable in order to secure orphan drug benefits or other types of marketing exclusivity. Consequently, business considerations rather than safety concerns may drive a request for a particular designation.[180] Furthermore, unclear regulations can also result in unnecessary delay and expenses. To solve these problems, we propose the following suggestions.

A. *Regulating Combination Products Based on "Novel Mode of Action"*

There is concern that the increasingly challenging and inefficient regulatory regime, combined with an ever more costly drug development process, is preventing pharmaceutical pioneers from fully realizing the benefits of many scientific discoveries made in recent years.[181] Some argue that the regulatory nature of FDA prevents it from being as innovative as the technology it regulates.[182] However, FDA should not be an obstacle to innovation. While the agency cannot lead innovation, it should at least actively monitor emerging technologies and modify its regulations to address the challenges presented by the industry.

Currently, the algorithm used by the Office of Combination Products assigns combination products to a lead center based on the product's "primary mode of action."[183] However, this algorithm is flawed because it ignores the importance of the novel aspects of the technology in a combination product. Since typical smart pills are drugs combined with drug-delivery systems, the OCP will almost always assign such a product to CDER. In general, the device component in a smart pill merely serves to enhance the mode of action of the drug component. However, if the device component of a smart pill uses novel technology, CDER will be ill-equipped to evaluate the safety and efficacy of the device. Consequently, it would be more appropriate for the OCP to determine a lead center by using an algorithm based on a product's "novel mode of action." If an old drug is combined with a new device, having CDER focus on evaluating the drug component for safety and efficacy adds little value. In this case, it would be more important to determine if the novel device component is suitable for marketing. If neither component or both components of the combination product are novel, then the OCP could evaluate the product's primary mode of action to determine a lead center.

Using a novel-mode-of-action algorithm should help eliminate uncertainty about how FDA will regulate smart pills while simplifying the approval process for many smart pill sponsors. In order to determine which center the OCP will assign a smart pill to, the sponsor merely needs to determine which component of the smart pill, if any, is novel. Because most smart pills will be relying on new medical device technology, it is likely that most smart pills would be assigned to CDRH under a novel-mode-of-action algorithm. And because CDRH regulatory requirements are typically much less stringent than CDER requirements, it should be quicker and cheaper for the sponsor to get marketing approval.

---

[179] *See* Rodney R. Munsey, *Trends and Events in FDA Regulating of Medical Devices Over the Last Fifty Years*, 50 FOOD & DRUG L.J. 163, 177 (1995); Lavender, *supra* note 37.

[180] *See* Lavender, *supra* note 37.

[181] *See* FDA, INNOVATION OR STAGNATION?: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS (2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4052B1_11_ExecSum-Critical-Path.pdf.

[182] *See* Foote & Berlin, *supra* note 62, at 644.

[183] *See supra* Part II.A.

B. *Creating a New Combination Product Application*

In order to streamline marketing approval for combination products, FDA should create a special application process specifically for these products. For example, the Agency could create a New Combination Product Application (NCPA), which would be similar to an NDA for drugs or a premarketing approval application for medical devices. The NCPA would be handled by the OCP. Further, the OCP would have jurisdiction over all combination products and be given the authority to grant marketing approval independent of CDER, CDRH or CBER.

FDA's current multi-center regulatory framework can be traced back to the Pure Food and Drug Act of 1906, where drugs were defined and separated from foods.[184] Throughout the 1960s, FDA tried to classify some devices as drugs but eventually moved the Office of Medical Devices out of the Bureau of Drugs in 1971.[185] Biologics were regulated in a parallel track from drugs and devices.[186] The multi-center framework, finalized by 1980, classified medical products into three distinct categories.[187] However, significant scientific development in the last twenty years has dissolved the traditional boundaries among drugs, devices, and biologics.[188] Consequently, many innovative products, such as combination products, do not fit neatly into these categories.

FDA tried to solve this problem by establishing the OCP. But the OCP operates by assigning combination products to one of the three centers. Further, the principle of designation is based on the definitions of drugs, devices, and biologics, and the combination products are still regulated under the traditional framework. Thus, by stretching the limits of the definitions, FDA tries to fit innovative products into the old regulatory framework. However, such efforts do not address the real issues associated with rapid technology development — the issues of ensuring the safety and efficacy of novel products while helping them reach the public in a timely manner. Instead, the function of the OCP seems focused on ensuring that the turf of one center is not invaded by another center.[189]

The ultimate solution is to give the OCP the power to independently regulate these innovative combination products. We suggest promoting the OCP from an office to a center, coequal with CDER and CDRH, with the authority to grant marketing approval to combination products without CDER or CDRH review.[190] The new center does not need to fit a hybrid technology into a drug or device category. Instead, the new center could regulate combination products according to the underlying technology. For example, smart pills would be regulated neither as drugs nor as devices, but instead as ingestible drug/device combination products; and the new center for combination products could design regulations that fit the particular needs of smart pills and other hybrid technologies.

This new "Center for Combination Products" could directly address many problems raised under the current framework. First, the review would be more

---

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

[185] *See* Foote & Berlin, *supra* note 62, at 628.

[186] *Id.*

[187] *Id.*

[188] *Id.*

[189] Foote & Berlin, *supra* note 62, at 640.

[190] *See* Kshitij Mohan, *Combination Products: Incrementalism Won't Work*, MED. DEVICE & DIAGNOSTIC INDUS., May 1, 2002, http://www.mddionline.com/article/combination-products-incrementalism-wont-work.

consistent because the sponsors only need to deal with a single center and that center could issue a single set of consistent regulations.[191] Second, the review process would be faster because unnecessary regulations and inter-center disputes could be eliminated. Third, the new center would be able to react more quickly to advances in technology and more ably facilitate innovations.

Creating a new center exclusively for combination products will not be easy. It may require legislative action and would be an expensive undertaking.[192] Furthermore, FDA lacks the manpower and funds for support an independent combination products center. The OCP is currently a small organization, a sub-office of the Office of Special Medical Programs, with only eight employees.[193] However, the new center could promote the development of innovative combination products. Reduced review time would benefit sponsors since time is essential for many innovative products.[194] Without inter-center disputes and overlapping regulations, the new center will likely be more efficient. Therefore, any initial costs could be offset over time.

C. *Eliminating Dual-Approval Requirements and Providing Industry Guidance*

FDA's mission is to protect public health by promoting innovations that make treatment more effective, safe, and affordable.[195] Because smart pills have the potential to make drugs safer and more effective, the agency should work to facilitate the development of smart-pill technology. To achieve this goal, FDA should provide clear guidance on regulating ingestible drug/device combination products. After FDA released guidance documents for drug-eluting stents, the number of drug-eluting stents receiving premarket approval increased significantly.[196] Similarly, guidance documents related to smart pills could greatly accelerate bringing these products to market.

As this article's analysis suggests, old drug/old device and old drug/new device combinations are the most likely scenarios for smart pill sponsors. Thus, FDA should carefully consider these two combinations and design appropriate guidance documents that address the specific regulatory questions and challenges faced by these products. The agency's guidance documents first need to clarify that the lead center to review the products is CDER so that consistency and certainty can be expected among products. Furthermore, FDA should specify the circumstance under which a full NDA, abbreviated NDA, or a section 505(b)(2) NDA is appropriate. Finally, FDA

---

[191] However, regulation by a new center devoted to combination products could be problematic it the new center regulates similar products differently than CDER or CDRH.

[192] *See* Lavender, *supra* note 37. Because combination products are defined by statute, see 21 U.S.C. § 353(g), legislation may be needed to redefine combination product to allow a new center regulate them. E-mail from Prof. Marsha Cohen, University of California, Hastings College of the Law, to Authors (Feb. 15, 2011) (on file with authors). However, some practitioners think legislation is not necessary because "FDA creates all kinds of bureaucratic organizations without legislative endorsement, and indeed the current organization of FDA is not created by statue." Email from Peter Barton Hutt, Senior Counsel, Covington & Burling LLP, in Wash., D.C. (July 27, 2011) (on file with authors).

[193] *See* FDA, Office of Combination Products, http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScienceandHealthCoordination/OfficeofCombinationProducts/default.htm; *see also* FDA, Office of Special Medical Programs Organization Chart, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM239674.pdf.

[194] *See* Lavender, *supra* note 37, at 4.

[195] *See* FDA, *What Do We Do,* http://www.fda.gov/aboutfda/whatwedo/default.htm.

[196] *See supra* note 135. Before 2008, FDA granted not more than twenty-five marketing approval of drug-eluting stents per year. Since the agency released a detailed guidance in 2008, the number of drug-eluting stents receiving marketing approval increased to over 80 per year.

should specify if and when additional safety, efficacy, pharmacology, or toxicology data is necessary for this class of products.

As discussed previously, a smart pill sponsor may submit marketing applications to both CDER and CDRH in certain situations, such as to obtain orphan drug status for a product that has been assigned to CDRH.[197] Dual applications impose extra burdens on both the sponsors and regulators.[198] Furthermore, many CDER and CDRH requirements for marketing approval are redundant. In order to facilitate development of combination products such as smart pills, FDA should modify regulations so that sponsors never have to seek marketing approval from more than one center. One set of requirements not only saves resources for FDA and sponsors, but will speed the review process. For scenarios where a sponsor may elect to file two applications in order to qualify a smart pill for certain benefits, such as orphan drug benefits, FDA should allow the sponsor to receive the benefit without filing a second application. Reducing regulatory fees and processing time can benefit patients too because they can receive the treatment earlier and possibly at lower costs. Thus, eliminating dual-approval requirements would benefit FDA, sponsors, and the general public.

CONCLUSION

Smart pills have the potential to revolutionize drug treatment with safer and more effective therapies. By coupling drugs with medical devices, it is possible to control and target the release of a drug, heightening efficacy and minimizing adverse effects.

While smart pills are a promising technology, their development is still nascent and their ability to reach the market is uncertain. The technical and regulatory complexities of developing an ingestible drug/device combination product may deter pharmaceutical companies from investing in smart pill research and development.

In order to help the smart pills currently being developed reach patients and to encourage firms to develop more creative combination products, the regulatory hurdles to developing smart pills must be removed. FDA should provide further guidance on requirements regarding clinical trial design, data submission, marketing approval and drug-diagnostic co-development. Also, current regulations must be redesigned to accommodate the unique challenges in developing a drug/device combination product. This can be done by issuing specific regulations on ingestible drug/device combination products that use an existing drug. Further, FDA should simplify regulations and eliminate dual-approval requirements. Ultimately, FDA should create a new combination product application and establish a new center with jurisdiction over combination products. This approach will solve many regulatory problems facing smart pills and other innovative combination products. Instead of following the drug and device frameworks, the new center could design and regulate according to the underlying techonology. Under the new regulatory scheme, review time will be greatly reduced and the process will become more efficient. Therefore, it will promote the development of innovative combination products and eventually benefit the general public.

---

[197] *See supra* Part II.C.

[198] *See* FDA, APPLICATION USER FEES FOR COMBINATION PRODUCTS, GUIDANCE FOR INDUSTRY AND FDA STAFF (2005), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147118.pdf.