

REGULATING INNOVATIVE MEDICINE: FITTING SQUARE PEGS IN ROUND HOLES

MARK LAVENDER¹

ABSTRACT

Increasingly, innovative medical products are creating a quandary for the Food and Drug Administration ("FDA") because they often transcend the FDA's traditional categorical approach to regulating medical products. In a recent attempt to simplify this process, the FDA has proposed a new rule for regulating "combination products." This iBrief discusses the FDA's current approach and analyzes the possible affects of the proposed regulation. Because of the many shortcomings of both systems, this iBrief concludes that the FDA should instead stop assigning center jurisdiction based on a product's "primary mode of action," and give the Office of Combination Products internal agency jurisdiction over combination products. This alternative approach would increase consistency and efficiency while maintaining the FDA's high standards for medical product safety and efficacy.

INTRODUCTION

¶1 Among other responsibilities, the United States Food and Drug Administration ("FDA") is charged with ensuring that medical products made or sold in the United States are safe and effective.² In effectuating this charge, the FDA assigns each product to one of three centers based on whether the product is a drug, biologic, or device.³ However, medical

¹ J.D. Candidate, 2006, Duke University School of Law; M.S. in Biomedical Engineering, 2003, Duke University; B.S.E. in Mechanical Engineering, 2000, University of Michigan - Ann Arbor. The author would like to thank Kimberly Dornbrook, Pharm.D., B.C.P.S.

² See Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 393(b)(2)(B)-(C) (2000) (referring to human drugs and devices intended for human use). The FDA is generally responsible for promoting "the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner." *Id.* § 393(b)(1).

³ See 21 U.S.C. § 360bbb-2(a). Broadly, the definitions for the three categories are as follows:

[A drug is an article] intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man . . . [or] . . . [an article] intended to affect the structure or any function of the body of man
21 U.S.C. § 321(g)(1).

products on the cutting edge of technology are increasingly crossing over at least two of these categorical lines. Consequently, these "combination products" face a hoard of regulatory snafus.

¶2 Within the FDA are three centers that oversee the pre-market review and post-market regulation of human medical drugs, biologics, and devices, namely, the Center for Drug Evaluation and Research ("CDER"), the Center for Biologics Evaluation and Research ("CBER"), and the Center for Devices and Radiological Health ("CDRH").⁴ Although these centers are under the umbrella of the FDA, they are autonomous organizations with their own staffs, standards, and cultures.⁵ When a new, easily classifiable medical product is researched and developed, it is submitted to the appropriate center for review.⁶ Novel, innovative products that incorporate aspects of two or three of the classifications, thus crossing traditional center designations, are termed "combination products."⁷ In many situations, the appropriate center for regulating a combination product is not certain.⁸

[A biologic is] a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Public Health Service Act, 42 U.S.C. § 262(i) (2000).

[A device is] an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease . . . or . . . intended to affect the structure or any function of the body . . . and which does not achieve its primary intended purposes through chemical action within or on the body . . . and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

21 U.S.C. § 321(h).

⁴ FDA Product Jurisdiction, 21 C.F.R. § 3.2(b) (2004).

⁵ See *OCB Bridging Center Cultures at One-Year Mark*, THE FOOD & DRUG LETTER, Mar. 26, 2004, at 6. The differences are so great that the FDA is even developing training programs for the different centers to better grasp each other's varying procedures, standards, and organization. *Id.*

⁶ See 21 U.S.C. § 360bbb-2(a).

⁷ 21 C.F.R. § 3.2(e). The regulation states that a combination product includes the following:

(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

¶3 According to the FDA, “combination products have the potential to make treatments safer, more effective, more convenient or more comfortable for patients.”⁹ Recent examples of approved combination products include: a fibrin sealant to assist sealing incisions received during surgery; a spinal fusion putty to help grow new spinal bone; a fibroblast-derived dermal substitute to cover, support, and grow new skin over a wound; and new drug-eluting stents to open and prevent the re-narrowing of arteries.¹⁰

and biological products, or biological and drug products;

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

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

Id. For the purposes of this paper, most of the discussion will focus on the first definition, where “two or more regulated components [are] physically, chemically, or otherwise combined or mixed and produced as a single entity.”

Id.

⁸ See 21 C.F.R. §§ 3.4(a), 3.2(b).

⁹ See FDA Talk Paper, *FDA Proposes Rule on “Combination” Products*, U.S. Food and Drug Admin., Pub. No. T04-13 (May 6, 2004), available at <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01288.html>.

¹⁰ *Recent Examples of Combination Product Approvals*, U.S. Food and Drug Admin., at <http://www.fda.gov/oc/combination/approvals.html> (last visited Sept. 22, 2004). In more detail, the FDA noted that

innovative drug delivery devices have the potential to make treatments safer or more effective, or more convenient or acceptable to patients. Drug-eluting cardiovascular stents have the potential to reduce the need for surgery by preventing the restenosis that sometimes occurs following stent implantation. Drugs and biologics can be used in combination to potentially enhance the safety and/or effectiveness of either product used alone. Biologics are being incorporated into novel orthopedic implants to help facilitate the regeneration of bone required to permanently stabilize the implants.

Overview of the Office of Combination Products, U.S. Food and Drug Admin., at <http://www.fda.gov/oc/combination/overview.html> (last visited Sept. 22, 2004).

¶4 In the future, combination products may well come to represent the most innovative products, as "research is being driven by the very concept of combinations."¹¹ These products will likely continue to blur the boundaries between drugs, biologics, and devices.¹² Because of the rising popularity and complexity of combination products, this iBrief reviews the FDA's current regulatory system surrounding these products. Further, it analyzes a recently proposed FDA rule that would codify a definition for a combination product's "primary mode of action." In conclusion, because of the many shortcomings of both the current arrangement and the proposed regulation, this iBrief suggests that the correct course of action is for the FDA to stop assigning center jurisdiction based on a product's "primary mode of action," and to give the Office of Combination Products internal agency jurisdiction over combination products.

I. THE CURRENT REGULATORY SITUATION

¶5 Currently, a combination product is routed to one of the FDA's regulatory product centers by the two-year old Office of Combination Products ("OCP").¹³ Its function is to "ensure the prompt assignment of combination products to agency centers, the timely and effective pre-market review of such products, and consistent and appropriate post-market regulation of like products subject to the same statutory requirements to the extent permitted by law."¹⁴ The OCP assigns a product to a center based on its "primary mode of action" ("PMOA").¹⁵ If the product's PMOA is determined to be that of a drug, biologic, or device, then the appropriate center for primary jurisdiction is the CDER, CBER, or CDRH, respectively.¹⁶ However, the term "primary mode of action"¹⁷ is not clearly defined by either statute or the FDA, and its application has caused

¹¹ *Combination Product Applications Increasing, Crossing Traditional FDA Medical Center Lines*, THE FOOD & DRUG LETTER, Mar. 26, 2004, at 1, 4 (quoting Janet Trunzo, senior vice president of global regulatory affairs at AdvaMed, a medical device trade group).

¹² *See id.*

¹³ The OCP was created by the Medical Device User Fee Modernization Act of 2002, Pub. L. No. 107-250, § 204, 116 Stat. 1588, 1611 (to be codified at 21 U.S.C. § 353(g)).

¹⁴ 21 U.S.C.A. § 353(g)(4)(A) (West 1999 & Supp. 2004).

¹⁵ *Id.* § 353(g)(1). PMOA itself is fairly new terminology, being created by the Safe Medical Device Act of 1990. Pub. L. No. 101-629, § 16(a), 104 Stat. 4511, 4526.

¹⁶ *See* 21 U.S.C.A. §§ 353(g)(1)(A)-(C).

¹⁷ *Id.* § 353(g)(1).

confusion.¹⁸ Adding to this uncertainty are the FDA's stipulation that the center with primary jurisdiction may consult with other centers, and the possibility that the FDA may require marketing applications to multiple centers.¹⁹ In essence, the FDA has too many cooks in the regulatory kitchen, which leads to inefficient, subjective, unpredictable, and costly outcomes. These snags in the system also fail to result in improved public safety.²⁰

¶6 There is no codified definition or method for determining a product's PMOA. Therefore, the FDA determines center jurisdiction for many innovative products on a case-by-case basis;²¹ the relevant features for determining PMOA may lie in the "eye of the beholder."²² Furthermore, the determination may be influenced by what the sponsor does or does not claim and how the product has been designed to achieve a certain therapeutic benefit.²³

A. Differences between product centers

¶7 There are substantial differences among the three FDA centers. For example, in their requirements to demonstrate efficacy, the CDER and CBER require at least one, randomized, placebo-controlled study, whereas CDRH has usually been more flexible and typically accepts other study

¹⁸ Editor's Page: *Unlocking the Future of Combination Products*, MEDICAL DEVICE & DIAGNOSTIC INDUSTRY, Dec. 2002, available at <http://www.devicelink.com/mddi/archive/02/12/001.html>.

¹⁹ 21 C.F.R. § 3.4(b).

²⁰ Kshitij Mohan, *Combination Products: Incrementalism Won't Work*, MEDICAL DEVICE & DIAGNOSTIC INDUSTRY, May 2002, at 52, available at <http://www.devicelink.com/mddi/archive/02/05/017.html> (conjecturing that the new regulations "end up delaying or denying benefits to patients without providing offsetting benefits of enhanced safety and effectiveness").

²¹ Barry S. Sall et. al, *Getting Started with a Combination Product: Part I*, MEDICAL DEVICE & DIAGNOSTIC INDUSTRY, Mar. 2003, at 54, available at <http://www.devicelink.com/mddi/archive/03/03/018.html>; see Sharon A. Segal, *Device and Biologic Combination Products: Understanding the Evolving Regulation*, MEDICAL DEVICE & DIAGNOSTIC INDUSTRY, Jan. 1999, at 180 ("Until [the FDA] establishes comprehensive and accurate processes for designating jurisdiction and determining a product's primary mode of action, the agency will continue to exercise its discretion on a flexible, case-by-case basis regarding the more-complex or problematic products."), available at <http://www.devicelink.com/mddi/archive/99/01/016.html>.

²² David Smith, *A Primer on Engineered Tissues and FDA Classification of Medical Products*, PITTSBURGH TISSUE ENGINEERING INITIATIVE, available at <http://www.ptei.org/Industry/FDAPrimer.asp> (last visited Sept. 25, 2004).

²³ *Id.*

designs.²⁴ Other differences between the centers include the following: "statutory differences in approval times, . . . a greater likelihood of securing approval for a product if it is designated as a device, . . . [and a] manufacturer may be more familiar with a particular center or . . . want to target a particular center for its tendency to evaluate certain types of evidence"²⁵

¶8 The classification of a medical product can have far-reaching effects. A device classification may insulate a manufacturer from product liability litigation, whereas a drug or biologic classification does not afford such protection under the auspices of the Federal Food, Drug, and Cosmetic Act.²⁶ For the 2005 fiscal year, application fees will also vary significantly among the different FDA combination product classifications; at their highest levels, device user application fees cost about \$240,000,²⁷ whereas user drug and biologic application fees cost over \$670,000.²⁸

¶9 *Bracco Diagnostics, Inc. v. Shalala*²⁹ exemplifies the negative effects of product classification. In this case, ultrasound contrast agents, a device-drug combination product, were predominately assigned to the CDER, but one manufacturer's product was assigned to the CDRH.³⁰ The pre-market review process differences were highlighted by one manufacturer's comments: "The usual development of a device takes less time than development as a drug. It requires fewer patients and less safety and efficacy data. This results in development cost savings and increased development speed."³¹ Additionally, in 1997, two of the manufacturers that had their products reviewed by the CDER had already incurred \$1.5 million

²⁴ Alison Lawton, *An Industry Perspective on Regulatory Oversight of Cell and Tissue Based Products*, 2000 PROC. WTEC WORKSHOP ON TISSUE ENGINEERING RES. U.S. 240-41, available at <http://wtec.org/loyola/te/usws/usws-07.pdf>.

²⁵ John Miller, *Beyond Biotechnology: FDA Regulation of Nanomedicine*, 4 COLUM. SCI. & TECH. L. REV. 5, at *23 (Apr. 23, 2003), available at <http://www.stlr.org/cite.cgi?volume=4&article=5> (footnotes omitted).

²⁶ David Smith, *Legal and Regulatory Issues*, 2002 WTEC PANEL REPORT ON TISSUE ENGINEERING RES. 81, 83, available at http://wtec.org/loyola/te/final/te_final.pdf; see 21 U.S.C. §§ 1601-1606 (2000).

²⁷ Establishment of Medical Device User Fee Rates for Fiscal Year 2005, 69 Fed. Reg. 46,153, 46,155 (Aug. 2, 2004).

²⁸ Establishment of Prescription Drug User Fee Rates for Fiscal Year 2005, 69 Fed. Reg. 46,165, 46,168 (Aug. 2, 2004).

²⁹ 963 F. Supp. 20 (D.D.C. 1997).

³⁰ *Id.* at 24.

³¹ *Id.* at 29.

and \$3.7 million more in expenses than if their products had been assigned to the CDRH.³²

¶10 In addition to initial discrepancies between the regulatory pathways and user fees at each of the centers, there are more subtle differences. For instance, if a product is classified as a biologic or a drug, it can obtain "orphan drug" status, which provides numerous benefits.³³ However, if the product is considered a device, it can only obtain a "humanitarian device exemption."³⁴ The most significant difference between the two designations is that a humanitarian device can only be intended to treat a disease that affects fewer than 4,000 people in the United States while an orphan drug can intend to treat a disease that affects up to 200,000 people.³⁵ In addition, an orphan drug can be granted market exclusivity for seven years from the date of FDA approval, which is typically longer and less expensive than the exclusivity obtainable by a patent.³⁶ An orphan drug can also receive "certain tax credits for clinical research expenses; cash grant support for clinical trials; and waiver of the expensive prescription drug filing fee."³⁷

¶11 After a medical product's approval, its classification has effects outside the FDA's immediate sphere of influence. For instance, sales representatives for drugs and devices are treated differently by hospitals and clinics; while drug representatives are typically restricted, device representatives have "almost unlimited access to their physician customers."³⁸

¶12 Stepping back inside the doors of the FDA, there can be problems when a center obtains primary jurisdiction over a product with which it has limited familiarity. The "designated center could very well lack necessary information regarding components of the product that are outside its area of

³² See *Id.* at 29 n.9. Ultimately, the court held that when regulating and reviewing a combination product, the FDA has discretion in how to treat the product, but it is not allowed to treat two similar products dissimilarly on two different regulatory tracks, without legitimate justification. *Id.* at 28.

³³ Smith, *supra* note 26, at 84.

³⁴ *Id.*

³⁵ *Id.*

³⁶ *Id.*

³⁷ *Id.*

³⁸ Fred Gebhart, *Do Combination Products Spark Turf Wars? Hospital Practice.*, DRUG TOPICS, Oct. 7, 2002, at 42. A manufacturer of a drug orthopedic sleeve stated that "[a]pproval as a device is crucial to physician access and to our sales effort." *Id.* (quoting Andrew Burns, spokesman for Smith & Nephew, a medical device manufacturer).

expertise."³⁹ However, the FDA has procedures and mechanisms in place intended to help alleviate these concerns.

B. Inadequate agreements

¶13 Presently, the FDA attempts to bolster its assignment of combination products through intercenter agreements, which are documents the FDA has promulgated to clarify product jurisdiction questions between two centers.⁴⁰ Originally created in 1991, the agreements "describe the allocation of responsibility, by center, for categories of products or specific products which are a biologic, a device, or a drug."⁴¹ They also describe methods for resolving disputes and conducting collaborative reviews.⁴²

¶14 Unfortunately, the agreements are behind the times. In 2002, the FDA realized this problem and called for a public hearing on the topic,⁴³ stating, "[w]hile the Intercenter Agreements continue to provide useful guidance, the evolution in technology and scientific knowledge about the mode of action of medical products has in some cases pushed the usefulness of the current Intercenter Agreements past their limits."⁴⁴ Unfortunately, the FDA will likely answer questions regarding combination products slowly, as the Agency itself is uncertain about the "process and leadership traceable to the inadequacy of the intercenter agreements" and because of the recent creation of the OCP.⁴⁵

³⁹ Segal, *supra* note 21.

⁴⁰ 21 C.F.R. § 3.5(a)(1). The titles are as follows:

“Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health;”

“Intercenter Agreement Between the Center for Devices and Radiological Health and the Center for Biologics Evaluation and Research;”

“Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research.”

Id. The agreements are available at the following internet address:

<http://www.fda.gov/oc/combinatiion/intercenter.html> (last visited Sept. 22, 2004).

⁴¹ Assignment of Agency Component for Review of Premarket Applications; Guidance Documents Entitled Intercenter Agreements for Biologic, Device and Drug Products; Availability, 56 Fed. Reg. 58,760, 58,760 (Nov. 21, 1991); *see* 21 C.F.R. § 3.5(a)(2).

⁴² *Id.*

⁴³ *See* FDA Regulation of Combination Products; Public Hearing, 67 Fed. Reg. 65,801 (Oct. 28, 2002).

⁴⁴ *Id.* at 65,802.

⁴⁵ Ken Sumner, *Attitude Adjustment*, MX, May/June 2003, available at <http://www.devicelink.com/mx/archive/03/05/sumner.html>.

¶15 The intercenter agreements are only useful if a product's characteristics are clear or specifically listed in the agreements; if not, the agreements can be vague and difficult to understand.⁴⁶ Contributing to this quandary is the fact that the agreements are not binding,⁴⁷ and do not cover the increasingly common situation where a combination product encompasses the characteristics of a drug, a biologic, and a device because the agreements are only between two centers, not three—there is no tripartite agreement for a medical product having characteristics of all three categories. Therefore, while the agreements are a good attempt to solve past jurisdictional questions, they are not equipped to handle new, innovative products that encompass technologies not yet envisioned.

C. Time delays

¶16 If a product is not listed in the appropriate intercenter agreement or if the proper center is uncertain, a sponsor can file a Request for Designation ("RFD").⁴⁸ The sponsor provides information in the RFD to inform the FDA which center it believes would be the most appropriate.⁴⁹ While an RFD may be useful to third parties who are similarly situated with a similar product, the filings "are highly confidential, just [knowledge of] the existence of a letter would give away a significant trade secret."⁵⁰ Therefore, the general lack of guidance for innovative products can also be attributable to confidentiality concerns.⁵¹ Also, the FDA's decision on an RFD is not binding, and requests are determined on a case-by-case basis.⁵² For all of these reasons, the regulatory statuses for advanced medical technologies can remain unknown for extended periods of time.⁵³

⁴⁶ Mary McNamara-Cullinane, *Understanding the Request for Designation (RFD) - A Critical Step in the FDA Regulatory Process for Combination Products*, REGULATORY, CLINICAL, & COMPLIANCE NEWSLETTER (Medical Device Consultants, Inc., North Attleboro, Mass.), Mar. 2004, at http://www.mdci.com/pages/nwsltr_0403.html.

⁴⁷ 21 C.F.R. § 3.5(a)(2).

⁴⁸ *Id.* §§ 3.5(b), 3.7.

⁴⁹ *Id.* § 3.7(c)(2)(ix).

⁵⁰ *Flexible, Tailored Regulation Seen as Combo Product Key*, THE FOOD & DRUG LETTER, Aug. 15, 2003 (modification in original) (quoting Mark Kramer, director of the FDA's Office of Combination Products) (available on Lexis).

⁵¹ Sall et al., *supra* note 21, at 54.

⁵² *Id.*

⁵³ *Id.*; see Miller, *supra* note 25, at *25 (stating that the process for determining primary jurisdiction is "time-intensive").

¶17 For most medical products, especially innovative combination products, time is of the essence.⁵⁴ Among other things, delays in the regulatory process can delay or destroy projects, diminish investors' returns, and impact millions of people's lives by delaying or denying access to innovative products.⁵⁵ In fact, stakeholders have become frustrated because innovation in this field is far outpacing regulatory approvals;⁵⁶ the current combination product regulatory approach has even been declared "woefully inadequate" by one commentator.⁵⁷ The PMOA process may be logical, but it is not practical as it does not allow for effective assignment "based on center resources and expertise."⁵⁸

¶18 Further adding to the consternation of moving a combination product through the FDA, a product sponsor can be certain that they will encounter numerous entities within the Agency. Not only are there potentially two product centers to interact with, but the Office of the Ombudsman, which used to handle the OCP's functions, is still involved even after the creation of the OCP;⁵⁹ thus, a sponsor must interact with the center having primary jurisdiction, potentially one or two consulting centers, the Office of the Ombudsman, and the OCP.⁶⁰ A non-combination medical product, such as a straightforward drug, biologic, or device, would not have to navigate the same maze, bypassing the combination product regulations.

D. Taking care of business

¶19 The ambiguity created when attempting to classify cutting-edge technology has led business considerations, rather than safety concerns, to drive the decision of which center a sponsor will suggest for jurisdiction.⁶¹ One consultant advises companies to position their products to increase the

⁵⁴ Gail Naughton, *An Industry Imperiled by Regulatory Bottlenecks*, 19 NATURE BIOTECHNOLOGY 709, 709 (2001).

⁵⁵ *Id.* at 709.

⁵⁶ *Id.* at 710.

⁵⁷ Editor's Page: *Unlocking the Future of Combination Products*, *supra* note 18

⁵⁸ *Id.* (quoting Suzanne O'Shea, Product Jurisdiction Officer in the FDA's Office of the Ombudsman).

⁵⁹ Sumner, *supra* note 45. The Office of the Ombudsman now determines if a product is a combination product, while the OCP assigns product jurisdiction and sets appropriate policies. *Id.*

⁶⁰ *Id.*

⁶¹ See Sall et al., *supra* note 21, at 54 (stating that "the developer must select which center to propose for primary jurisdiction" and that "[b]usiness considerations frequently drive this decision").

chance of "obtaining a favorable jurisdictional decision."⁶² Such advice is only a logical outcome from an amorphous regulatory situation because investors and company management want to know what type of medical product company they are dealing with—drug, biologic, or device—as this determination will establish the timeline for their revenue stream.⁶³ In addition, because precedent is not binding, the company must be prepared to justify product classification to *all* of the possible product centers.⁶⁴

E. Looking forward

¶20 It is important to be aware of significant developing medical technology fields where combination products will play a large role. Tissue engineering is such a field worthy of attention, for not only the innovative medical advancements it encompasses, but also for financial reasons. One study forecasted that the tissue engineering market will develop into an annual \$196 billion industry by 2013.⁶⁵

¶21 Tissue engineering is a broad field that is difficult to narrowly define.⁶⁶ One of the more straightforward definitions states that tissue engineering is "the persuasion of the body to heal itself through the delivery to the appropriate sites, of molecular signals, cells, and supporting structures."⁶⁷ These three areas correlate with the FDA's product centers; therefore, tissue engineered products have the potential to cross all three lines of the FDA's categorical approach. In fact, one commentator

⁶² McNamara-Cullinane, *supra* note 46. A favorable decision is often viewed as occurring when the FDA assigns a combination product to the CDRH. *FDA Defines 'Primary Mode of Action' for Combination Products*, GUIDE TO MEDICAL DEVICE REGULATION (Thompson Publishing Group, Inc., Washington, D.C.), June 2004, at

<http://www.thompson.com/libraries/fooddrug/xray/sampleneews/xray0406.html>.

Prior to the Agency's rule proposal regarding a product's PMOA, an industry group urged the FDA for "maximum use of device jurisdiction and authorities," noting that the CDRH had received "years of combination product assignments." *Id.*

⁶³ Sall et al., *supra* note 21, at 54.

⁶⁴ *Id.*

⁶⁵ *Bio-Engineered Cardiovascular and Skin Repair and Replacement Products to Lead Growth in the U.S. and Worldwide Tissue Engineering Markets*, According to Medtech Insight Analysis, BUSINESS WIRE, Aug. 9, 2004 (available on Lexis).

⁶⁶ JACQUELINE SENKER, HUMAN TISSUE-ENGINEERED PRODUCTS: TODAY'S MARKETS AND FUTURE PROSPECTS: LEGAL SITUATION AND SOCIO-ECONOMIC IMPACTS OF TISSUE ENGINEERING 3 (April 2003), available at http://lifesciences.jrc.es/docs/TE_WP4_FinalReport.pdf.

⁶⁷ *Id.*

suggested that a better designation for tissue engineered products might be as "biodeviceuticals."⁶⁸

¶22 Such a biodeviceutical was involved in a critical tissue engineering patent that was recently listed as one of ten patents that "shook up society."⁶⁹ A product resulting from the patent would undoubtedly be a combination product: the patent covered regeneration of spinal tissue using "a sponge-like scaffolding filled with a special hydrogel containing adult stem cells."⁷⁰ The scaffolding and hydrogel would likely be considered medical devices and the cellular component would likely be viewed as a biologic.⁷¹

¶23 The FDA is actively engaged in developing rational product development pathways, but these must fit into the existing well-established statutory scheme for classifying medical products.⁷² Tissue engineered products do not fit well into this regulatory arrangement.⁷³

¶24 The Agency's classification has broader implications than just indicating the center with jurisdictional and approval pathways for a product.⁷⁴ The classification of tissue engineered products may cause those products' commercial development to be more dependent on the regulatory approval process than on clinical outcomes.⁷⁵ The inconsistencies in the regulatory process "would increase the complexity of introducing new medical technologies incorporating human tissues without materially advancing public health or safety."⁷⁶

¶25 Tissue engineering products are usually assigned to either the CBER or the CDRH, which have different statutory standards for

⁶⁸ Naughton, *supra* note 54, at 709. (adding that these are "products that replace a tissue, tissue component, or a whole organ, which are bio-interactive and respond to the physiological needs of their local environment").

⁶⁹ Alan Cohen, *10 Patents That Changed the World*, IP WORDWIDE, Aug. 8, 2002, at <http://www.law.com/jsp/article.jsp?id=1028321279955>.

⁷⁰ Alan Cohen, *Not Quite the Bionic Man*, IP WORDWIDE, Aug. 8, 2002, at <http://www.law.com/jsp/article.jsp?id=1028321282569>.

⁷¹ See Segal *supra* note 21 (noticing that a similar product, combining cells and scaffolding to treat skin wounds, met the requirements for a biologic and a device).

⁷² Smith, *supra* note 26, at 81.

⁷³ *Id.*

⁷⁴ *Id.* at 82.

⁷⁵ *Id.* at 94.

⁷⁶ David Smith, *Introduction to Legal and Regulatory Issues*, 2000 PROC. WTEC WORKSHOP ON TISSUE ENGINEERING RES. U.S. 225, 227 available at <http://wtec.org/loyola/te/usws/usws-07.pdf>.

determining safety and efficacy.⁷⁷ The CDRH looks at whether a product is "safe and effective,"⁷⁸ whereas the CBER looks at a product's "saf[ety], pur[ity], and poten[cy]."⁷⁹ One researcher cited this difference among others in stating that the ability to take a tissue engineered product "from 'bench to bedside' is fraught with a litany of administrative guidelines."⁸⁰ The scientist noted that these products must comply with the CBER's drug-like requirements of demonstrating a product's "dose and potency."⁸¹ There are difficulties in proving these conditions for tissue engineered products which incorporate living cells.⁸² This problem does not exist under the device standards of the CDRH.⁸³

¶26 Tissue engineering exemplifies the trials and tribulations that must be overcome to bring a modern medical combination product to market. Unforeseen innovative technologies would likely encounter similar hurdles if the regulatory situation remains static. In light of these growing concerns, the FDA has not sat idle.

II. THE FDA'S SOLUTION

¶27 In May 2004, the FDA proposed a new rule to address many of the matters discussed above.⁸⁴ The proposed rule's purpose is two-fold: "(1) to codify . . . the criterion the FDA has used for more than a decade when assigning combination products to a particular Center within the agency for review; and (2) to simplify the assignment process."⁸⁵ In addition, the FDA explained, the new rule should "promote the public health by codifying the agency's criteria for the assignment of combination products in transparent, consistent, and predictable terms."⁸⁶ Unfortunately, the new rule does not

⁷⁷ See Smith, *supra* note 22 (stating that "there may be some subtle variation in the measurement of [safety and efficacy] among the FDA Centers").

⁷⁸ Smith, *supra* note 26, at 87; see 21 U.S.C. § 360c(a)(1).

⁷⁹ Smith, *supra* note 26, at 88; see 42 U.S.C. § 262(a)(2)(C)(i)(I).

⁸⁰ Kenji Izumi et al., *Development of a Tissue-Engineered Human Oral Mucosa: From the Bench to the Bed Side*, 176 *CELLS TISSUES ORGANS* 134, 149 (2004).

⁸¹ *Id.*

⁸² *Id.*

⁸³ *Id.*

⁸⁴ Definition of Primary Mode of Action of a Combination Product, 69 Fed. Reg. 25,527 (proposed May 7, 2004) (to be codified at 21 C.F.R. pt. 3) [hereinafter Rule Proposal].

⁸⁵ FDA Talk Paper, *supra* note 9.

⁸⁶ Rule Proposal, *supra* note 84, at 25,527.

generate the reform required for the regulation of combination products. As of December 31, 2004, the rule had not been adopted.⁸⁷

A. *The proposal*

¶28 The FDA's proposal would amend its current regulations in two substantive parts. First, the proposed rule would codify a definition for a product's PMOA,⁸⁸ the statutory standard that determines which product center has jurisdiction for a combination product.⁸⁹ Second, a two-tiered algorithm would be implemented when a product's PMOA is not evident.⁹⁰

¶29 The proposal explains that a product's PMOA is "the single mode of action of a combination product that provides the most important therapeutic action of the combination product."⁹¹ The most important therapeutic action is defined as "the mode of action expected to make the greatest contribution to the overall therapeutic effects of the combination product."⁹² "Mode of action" is categorized as either that of a drug, biological product, or device.⁹³ In the process of formulating the proposal, stakeholders informed the FDA that the PMOA should focus on the product as a whole, and the Agency agreed,⁹⁴ stating that the PMOA assignment will be based on the most important therapeutic action of the product *as a whole*.⁹⁵

¶30 Novel products that combine aspects of a drug, biologic, or device will not always have a single mode of action that provides the most important therapeutic action.⁹⁶ In these cases, the FDA's assignment algorithm fills the gap. This two-tiered algorithm is spelled out in the proposed rule as follows:

[T]he agency will assign the combination product to the agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the

⁸⁷ For up-to-date information on the status of the new rule see <http://www.fda.gov/oc/combo>.

⁸⁸ *Id.* at 25,528. The rule proposal also defines "mode of action," which would only apply to a portion of a combination product, as combination products typically will have more than one mode of action. *Id.*

⁸⁹ 21 U.S.C.A. § 353(g)(1).

⁹⁰ Rule Proposal, *supra* note 84, at 25,528.

⁹¹ *Id.* at 25,532 (proposed section 3.2(m)).

⁹² *Id.*

⁹³ *Id.* (proposed section 3.2(k)).

⁹⁴ *Id.* at 25,528.

⁹⁵ *Id.* However, the "as a whole" terminology was not included in the proposed rule. *See id.* at 25,532 (proposed section 3.2(k)).

⁹⁶ *Id.* (proposed section 3.4(b)).

combination product as a whole. When there are no other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole, the agency will assign the combination product to the agency component with the most expertise related to the most significant safety and effectiveness questions presented by the combination product.⁹⁷

¶31 Practically speaking, the proposed assignment system would first identify the combination product's modes of action and then ask a series of threshold questions as follows:

1. "Which mode of action is the most important therapeutic action of the combination product?";⁹⁸
2. "Is there an agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole?";⁹⁹ and
3. "Which agency component has the most expertise related to the most significant safety and effectiveness questions presented by the combination product?"¹⁰⁰

¶32 The rule proposal also included three examples for assigning products. These examples included analysis of a "conventional drug-eluting stent", a "drug-eluting disc", and a "contact lens combined with a drug to treat glaucoma."¹⁰¹ The examples designated jurisdiction to the CDRH, CDER, and CDER, respectively.¹⁰² There was not an example of a product being assigned to the CBER.

⁹⁷ *Id.* "Agency component" refers to either the CDER, CBER, or CDRH. 21 C.F.R. § 3.2(b).

⁹⁸ Rule Proposal, *supra* note 84, at 25,533 (visually outlining the proposed assignment system).

⁹⁹ *Id.*

¹⁰⁰ *Id.*

¹⁰¹ *Id.* at 25,529-30.

¹⁰² *Id.*

B. The response

¶33 Two industry groups, AdvaMed¹⁰³ and BIO,¹⁰⁴ filed comments regarding the proposed rule. First, the associations felt that it was important that the new rule more directly address the role of FDA jurisdictional precedents.¹⁰⁵ Second, the groups advised the Agency to further clarify how it would evaluate the PMOA by considering the combination product as a whole.¹⁰⁶ Third, AdvaMed desired that the last tier of the assignment algorithm focus "on the [the center with the] most significant safety and effectiveness questions presented by the combination product" instead of on "the [center with the] most expertise related to the most significant safety and effectiveness question presented by the combination product."¹⁰⁷ Lastly, both associations expressed concerns with the simplicity of the examples that the FDA had included in the rule proposal.¹⁰⁸

C. The new rule does not substantially change the situation

¶34 Despite the best efforts of the FDA and the conscientious comments of industry groups, the new rule will not eliminate the concerns arising out of the current assignment system. In fact, the Agency and industry stakeholders appear to be mostly concerned with maintaining the status quo.

¶35 The FDA stated that the rule's criteria are the same as the Agency has used in the past; the rule will only formalize the process.¹⁰⁹ In the rule proposal itself, the FDA stated that the "[t]his proposal would *merely* clarify and codify principles the agency has generally used since section 503(g) [21 U.S.C. § 353(g)] of the act was issued in 1990."¹¹⁰ Despite the proposed

¹⁰³ AdvaMed is the Advanced Medical Technology Association and "represents more than 1,200 innovators and manufacturers of medical devices, diagnostic products, and medical information systems." Letter from Carolyn D. Jones, Associate Vice President of Technology & Regulatory Affairs, AdvaMed, to FDA, 1 (Aug. 20, 2004) [hereinafter AdvaMed Letter], available at http://www.advamed.org/publicdocs/cjones_ltr_8-20-04.pdf.

¹⁰⁴ BIO is the Biotechnology Industry Organization, and "represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations." Letter from Sara Radcliffe, Managing Director of Science and Regulatory Affairs, BIO, to FDA 1 (Aug. 20, 2004) [hereinafter BIO Letter], at <http://www.bio.org/reg/20040820.asp>.

¹⁰⁵ AdvaMed Letter, *supra* note 103, at 3; BIO Letter, *supra* note 104, at 2.

¹⁰⁶ AdvaMed Letter, *supra* note 103, at 7; BIO Letter, *supra* note 104, at 2.

¹⁰⁷ AdvaMed Letter, *supra* note 103, at 9.

¹⁰⁸ *Id.* at 10; BIO Letter, *supra* note 104, at 3.

¹⁰⁹ *FDA Unveils Plans on Combo Products*, THE BBI NEWSLETTER (American Health Consultants, Inc., Monvale, N.J.), June 1, 2004, at 180.

¹¹⁰ Rule Proposal, *supra* note 84, at 25,528 (emphasis added).

rule's intent "to clarify and shed some transparency on the process, [it] doesn't seem to change much."¹¹¹ The FDA has been following the same principles for almost 14 years; thus if it simply formalizes, clarifies, and codifies those processes that have been regularly utilized, there will be little substantive change to address the concerns raised above.

¶36 The vagueness of the statutory phrase "primary mode of action,"¹¹² which is the source of the problems discussed above, would not change. The concern with the current PMOA classification system is that "some subjectivity is necessary . . . yielding a lack of consistency, predictability and transparency."¹¹³ The ambiguity is intrinsic to the phrase itself. It assumes that every combination product which exists has a *primary* mode of action. Unfortunately, a combination product can have two or more "therapeutic actions" equally contributing to a product's "overall therapeutic effects."¹¹⁴ This can result in similar products being assigned to different centers, further decreasing the FDA's efficiency.¹¹⁵

¶37 The examples discussed in the rule proposal also confirm the subjectivity of the algorithm. In the rule proposal, two similar products, a drug-eluting stent and a drug-eluting disc were assigned to the CDRH and CDER respectively.¹¹⁶ The differing centers were assigned despite the fact that both products were implantable devices that used a drug to achieve a therapeutic effect.¹¹⁷

¹¹¹ Cindy Becker, *Combo Devices Blur FDA Lines*, MODERN HEALTHCARE, May 17, 2004, at 20.

¹¹² 21 U.S.C.A. 353(g)(1).

¹¹³ *Risk Should Drive Combo Product Jurisdiction, Industry Recommends*, DEVICES & DIAGNOSTICS LETTER, Dec. 2, 2002 (quoting Mark Hamblin, a researcher with Carnegie Mellon University) (available on Lexis).

¹¹⁴ See Rule Proposal, *supra* note 84, at 25,532 (proposed section 3.2(m)). For example, an "interactive wound-care product" (Apligraf, Organogenesis Inc.) combined living cells with scaffolding, forming a cellular interactive biologic-device product. Segal, *supra* note 21. The living cells comprise the biologic and the mechanical scaffolding comprises the device. *Id.* Both modes of action significantly contributed to the product's therapeutic function, as the cells accelerated healing by providing a therapeutic effect via interactions with the wound, and the scaffolding accelerated healing by providing a therapeutic effect via enhancement of the wound's mechanical strength. See *id.*

¹¹⁵ One commentator discusses just such a situation arising with interactive wound-care products where the acellular product (Regranex gel, OMJ Pharmaceuticals Inc.) was assigned to the CDER while the cellular product (Apligraf) was assigned to the CDRH. Segal, *supra* note 21.

¹¹⁶ Rule Proposal, *supra* note 84, at 25,529-30.

¹¹⁷ See *id.*

¶38 The other issues would also remain because the difficulty in determining a product's PMOA still exist. The proposed rule would still require an inefficient case-by-case analysis by multiple FDA offices and centers, maintain the questionable RFD process, and continue to result in significant product review and approval delays. Business recommendations rather than safety concerns would also still drive RFD letters for new innovative products. Further, the intercenter agreements have not been updated and, even if they were, would not likely help future, unforeseen products. Lastly, significantly disparate treatment for similar products regulated by different centers would persist. There would be differences in product liability, cost, available special designations, and expertise between the centers. Consequently, at best the assignment process would take additional time; at worst "the process [would] kill a promising technology because the time, expense, and uncertainty make development economically unacceptable."¹¹⁸

III. SOLUTIONS: BIG AND SMALL

A. Alternatives to the new rule under the current statutory scheme

¶39 Alternative solutions that would not require major modifications to the statutory scheme have been proposed. For example, industry representatives agree that the FDA could propose a number of alternative methods for determining jurisdiction by focusing on different categorical schemes.¹¹⁹

¹¹⁸ Mohan, *supra* note 20, at 52. The author goes on to criticize the multi-center approach because it involves the following: (1) "three mutually exclusive organizations", (2) "three disparate sets of legal and regulatory requirements," (3) human beings, and (4) "the diversity of imaginative combinations that these products entail." *Id.*

¹¹⁹ *Biotech Combination Product Makers Facing New Designation Issues at FDA*, THE FOOD & DRUG LETTER, Aug. 15, 2003 (available on Lexis). These alternative methods to determine jurisdiction included the following focal points:

Mode of use; Whether the product has a local, regional or systematic effect; Which component of the product presents the greatest risk; Primary mode of therapeutic action; Whether one component serves only as a vehicle to deliver a therapeutic; How similar products are regulated; What feature of the product predominates or represents the innovations; and Which center has the best clinical skills and expertise to assist the sponsor with clinical trial design.

Id.

¶40 Another proposal suggested the adoption of a "risk-based classification system."¹²⁰ In this arrangement, product center jurisdiction would be determined by evaluating "the element of the product that poses the greatest risk to patient safety . . . and 'which center has the greatest experience managing that risk.'"¹²¹ Alternatively, one researcher recommended a lengthy "88-item weighted checklist that evaluates critical characteristics of each product."¹²²

¶41 The problem with these approaches is that they are variations of the same theme: determining what is the most important aspect of a combination product for classification purposes. Despite the combination product program's objective to make certain that combination product review is as efficient as possible, the process will never be as efficient as with a non-combination product because the products are more complex and more than one center is involved.¹²³ The problems associated with using multiple centers will likely persist; multiple center applications, communications, and other extraneous transactions will continue to bog down the regulatory system for combination products. A completely new methodology and organizational arrangement is needed for products that blur the boundaries between the traditional categorizations of drugs, biologics, and devices.

B. New statute, new center, and a better approach

¶42 Initially, the source of the assignment problem must be addressed. Currently, much of the consternation stems from the difficulty in classifying a combination product. Whether PMOA or some other definition is adopted, classification would still be an issue. Which center should be assigned which combination products? In answering this question, it is important to realize that there is nothing special about the current categorizations between drugs, biologics, and devices.¹²⁴ One commentator

¹²⁰ *Risk Should Drive Combo Product Jurisdiction, Industry Recommends, supra* note 113.

¹²¹ *Id.* (quoting Owen Fields, associate director of worldwide regulatory affairs at Wyeth).

¹²² *Risk Should Drive Combo Product Jurisdiction, Industry Recommends, supra* note 113.

¹²³ Robert Drummond, *Combination Product Reform to Speed Reviews, Increase Accountability*, MEDICAL DEVICE & DIAGNOSTIC INDUSTRY, Apr. 2002, at 20, available at <http://www.devicelink.com/mddi/archive/02/04/013.html>.

Determining the best way to make center designations has been analogized to "measuring length to the fourth decimal place with a crooked ruler." Mohan, *supra* note 20, at 52.

¹²⁴ Mohan, *supra* note 20, at 52.

noted that "[t]he future of medical technologies should not be held hostage to history."¹²⁵ Therefore, the statutory provision mandating the FDA to assign jurisdiction based on a product's PMOA¹²⁶ should be eliminated. Doing so would remove the problem at its source.

¶43 Next, what is needed is not necessarily less regulation of combination products, but a less complex system. Removing the statutory authority and guidance for FDA regulation and review of combination products will create a vacuum for those tasks. Filling this void, the OCP should be more than just a gate-keeping service of the FDA. It should have internal agency jurisdiction over the products and directly oversee their pre-market review and regulation. In this sense, it would develop into another product center.

¶44 This view is well expressed by another commentator, Kshitij Mohan.¹²⁷ Mohan believes that the best place to initially reorganize the OCP is within the CDRH.¹²⁸ This center has had the most exposure to combination products over its history and is the most flexible of the three medical product centers.¹²⁹ The new OCP would draw a staff from an interdisciplinary team of personnel currently in the other three centers and utilize joint appointments for some scientists and reviewers.¹³⁰ Over time, the new OCP would develop into its own center.¹³¹

¶45 Sowing the seeds for a new medical product center should increase consistency in the regulation of novel combination products. This solution would improve the current situation by improving "healthcare through a more efficient partnership among FDA, academia, and industry to speed the introduction of beneficial new technologies."¹³² It also "could become a model for how all of FDA will evolve to meet the changing needs of the 21st century."¹³³

¶46 In addition, a new OCP or center would follow the FDA's ongoing efforts and the recently-announced 'Critical Path' initiative, which emphasizes clarifying the complex therapeutic development process and

¹²⁵ *Id.*

¹²⁶ 21 U.S.C.A. § 353(g).

¹²⁷ Mohan, *supra* note 20, at 52.

¹²⁸ *Id.*

¹²⁹ *Id.*

¹³⁰ *Id.*

¹³¹ *Id.*

¹³² *Id.*

¹³³ *Id.*

helping to speed innovation.¹³⁴ The new entity would not have to spend much time analyzing *where* in the FDA a combination product should be evaluated. The inefficiencies of requiring a sponsor to over-communicate with the FDA's numerous combination product-specific entities would be gone. The time lost from interacting with those entities and waiting for RFDs to be fulfilled would also be eliminated. Intercenter agreements, business driving jurisdictional decisions, and the major substantive product differences resulting from center assignment would be removed.

¶47 As with most major changes, there will undoubtedly be some resistance. A grandfather clause may be necessary to allay concerns amongst current stakeholders who may feel that it would be unfair to reassign their currently regulated or forthcoming products to the sole and direct authority of the new OCP. However, Congress may have to directly authorize this, as the court in *Bracco* held that the FDA is not free to place similar products on separate regulatory tracks without legitimate reason.¹³⁵

¶48 Also, many companies rely on classifications to determine their sales strategies and they may negatively react to moving future products into a new center or new OCP. For instance, device sales representatives currently have better physician access than do drug sales representatives.¹³⁶ Therefore, changing the regulatory scheme by doing away with a combination product's primary association with the CDER, CBER, or CDRH could be resisted by industry because of its current business model.

¶49 On the government's tab, creating a new OCP or center will not be inexpensive. The staff, reorganization, and start-up costs may be high. Currently the FDA lacks sufficient funds to move combination products forward.¹³⁷ Additionally, FDA regulatory staff size has decreased while the number of pre-market approvals has increased.¹³⁸ The director of the CDRH estimates that half of the staff currently in the center will retire or resign in between 2006 and 2011.¹³⁹ The director's biggest challenge is to obtain sufficient funding "to hire qualified reviewers."¹⁴⁰ Consequently,

¹³⁴ See FDA, CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS iv (2004), available at <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>.

¹³⁵ *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 28 (D.D.C. 1997).

¹³⁶ Gebhart, *supra* note 38, at 42.

¹³⁷ Naughton, *supra* note 54, at 710.

¹³⁸ *Id.*

¹³⁹ *Id.*

¹⁴⁰ *Id.* (quoting *Advamed Urges FDA to Create New Combination Products Office*, DEVICES & DIAGNOSTICS LETTER, June 22, 2001 (quoting David Feigal, director of the CDRH)).

manpower and funds will be lacking across the board at the FDA and reorganizing a new regulatory body will be difficult.

¶50 However, these expenses can likely be absorbed in two ways. First, if Mohan's advice is followed and the new regulatory body is created within the CDRH, then much of the overhead for starting a new center should be reduced. Second, if combination products reach their market potential, then the increased user fees, combined with a more efficient combination product regulatory scheme, should help fund additional costs.

CONCLUSION

¶51 For combination products, the current multi-center assignment system, utilizing a product's "primary mode of action," should be eliminated and the OCP should be more than just a gate-keeping service of the FDA. Specifically, the OCP should have internal agency jurisdiction over combination products and oversee their review and regulation by drawing on the strengths of the other three centers. Keeping combination products within the redesigned OCP should increase consistency in the regulation of these novel products. This solution will improve the current situation and follow the FDA's ongoing efforts and recently-announced 'Critical Path' initiative, which emphasizes further clarifying the complex therapeutic development process and helping to speed innovation.