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Letter from the Editors

Dear Reader:

On behalf of the Editorial Board and staff, we proudly present Volume 10, Issue 2 of the *Health Law & Policy Brief* (HLPB). HLPB is an online publication run by law students at American University Washington College of Law (WCL). Since its formation in 2007, HLPB has published articles on a wide array of cutting-edge topics in the areas of health law, disability law, and food and drug law. Such topics include international and domestic issues of health care compliance, fraud and abuse enforcement, health insurance payment and reimbursement issues, intellectual property issues, international human rights issues, FDA initiatives and policies, and a host of other matters. HLPB also maintains a blog on current health law issues which can be found on our website at www.healthlawpolicy.org.

This issue features two timely articles. Our first author, Shruti Modi, discusses the emerging field of combination products and companion diagnostics and how the FDA regulates them. She analyzes the current regulatory regime for companion diagnostics and recommends that the FDA create an Office of Companion Diagnostics to help organize and clarify how companion diagnostics and their corresponding therapeutic products are regulated.

Our second author, Katelen Walsh, analyzes how FDA press releases containing adverse publicity can be harmful to the products' manufacturers, occasionally compelling the manufacturers to voluntarily withdrawing the product. She argues that the FDA must exercise care and minimize unnecessary harm to manufacturers and consumers. Katelen explains how we can improve the FDA's ability to make public statements that effectively protect consumers from dangerous products without unduly punishing manufacturers with unreasoned adverse publicity.

Both articles are timely and important to current health law and policy. We would like to thank our authors for their hard work and cooperation.

We would also like to thank HLPB's articles editors and staff members who worked diligently on these articles, the blog, and our programming throughout the year. They are greatly appreciated and should be proud of their work.

For questions or information about the *Health Law & Policy Brief*, or for questions on how to subscribe to our electronic publication, please visit our website at www.healthlawpolicy.org.

Sincerely,
Mohammad and Kate

Mohammad H. Mesbahi
Editor-in-Chief

Katharine Burmeister
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When Worlds Collide: Drugs And Devices

Shruti Modi[*]

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INTRODUCTION

Individuals experience disease and respond to treatment differently.[1] Accordingly, medical practitioners currently follow a trial-and-error approach when treating patients.[2] In other words, if a patient has a disease, his or her doctor will prescribe a treatment plan based on general information and re-assess after a few weeks.[3] If the treatment is not working, the doctor will change some variable in the plan, and wait a few more weeks to see if there is any improvement.[4] This approach can lead to patient dissatisfaction, adverse drug responses and drug interactions, and poor adherence to treatment regimens.[5] While this may seem bleak, rapid developments in a variety of medical fields like genomics, medical imaging, and computational biology are making it possible for scientists and doctors to personalize diagnosis and treatment of diseases.[6] Thus, the practice of medicine is becoming more personalized. The term "personalized medicine" is often described as providing "the right patient with the right drug at the right dose at the right time."[7] The Food & Drug Administration (FDA) describes personalized medicine as "the tailoring of medical treatment to the individual characteristics, needs and preferences of a patient during all stages of care, including prevention, diagnosis, treatment and follow-up."[8]

Personalized medicine usually involves the use of two medical products to improve patient outcomes.[9] These products may be diagnostic devices, therapeutic drugs, or biological products.[10] A diagnostic device is a medical device that is used to identify the presence, absence, or amount of a biomarker (as in the case of *in vitro* diagnostics) or to assess physiological or anatomical patient characteristics.[11] "Companion" diagnostic devices are becoming increasingly important to the development of drugs. Companion

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[1] FDA, *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development* 5-6 (2013), http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf.

[2] *Id.* at 6.

[3] *Id.*

[4] *Id.*

[5] *Id.* While there are some benefits to the trial-and-error approach, this approach is unable to exactly diagnose a disease at its outset, lengthening the amount of time before a disease is either cured or manageable. This approach identifies what is most likely to be the disease, and then experiments with varying treatments until one works. Precision medicine offers a more exact diagnosis at an earlier stage of a disease, taking into account specific and personal characteristics of each patient.

[6] *Id.*; *see also* Mayo Clinic, *Consumer Health: Personalized Medicine and Pharmacogenomics* (Jul. 14, 2012), http://www.mayoclinic.org/healthy-living/consumer-health/in-depth/personalized-medicine/art-20044300 (describing how to use trial and error to find the best treatment for a particular patient).

[7] FDA, *Paving the Way for Personalized Medicine*, *supra* note 1 at 6.

[8] *Id.*

[9] *Id.* at 2.

[10] *Id.*

[11] *Id.* at 10; *see also* Kyle Strimbu and Jorge A. Tavel, *What Are Biomarkers?*, Curr. Opin. HIV AIDS 463-66 (2010) (describing the potential for biomarkers to speed drug development and reduce exposure to ineffective and experimental treatments).

diagnostics are usually *in vitro* medical devices that provide information necessary for "the safe and effective use of a corresponding drug or biological product."[12] These help health care providers determine the risks and benefits of a particular drug for a patient.[13] Specifically, companion diagnostics can: 1) identify patients who will most likely benefit from a particular drug; 2) identify patients who will likely be at an increased risk for serious side effects from a drug; and 3) monitor patient responses to treatments with a drug to adjust treatment to achieve improved safety or efficacy. Companies are developing companion diagnostics for use in earlier stages of drug development and are co-developing drugs and companion diagnostic tests.[14]

In addition to companion diagnostics, the FDA states that combination products also fall under the personalized medicine umbrella.[15] Combination products are becoming more prevalent and important in treating patients. Combination products are diagnostic and therapeutic medical products that combine biological products, drugs, and/or devices because several are necessary to achieve the indication.[16] Some examples of approved combination products are drug-eluting stents for clogged heart arteries, surgical mesh with antibiotic coating, and drug patches used to treat depression.[17] These innovative combination products improve on previous products by using new and more tailored methods to treat disease quickly and effectively.

These tailored methods are potentially more effective at preventing and treating diseases, therefore easing patients' burdens. For instance, by improving the ability to predict and account for individual differences in disease diagnosis, experience, and therapy response, personalized medicine can diminish the severity of disease, shorten product development timelines, and improve success rates.[18] With the help of personalized medicine, health care management can focus more on wellness and maintaining health, rather than on illness and treating disease.[19] Furthermore, personalized medicine can reduce healthcare costs by improving the ability to reliably select effective therapy for a patient while minimizing the costs of ineffective treatments and the risk of avoidable adverse events.[20]

The FDA plays a crucial role in the future of personalized medicine. The FDA has specific and distinct regulatory pathways for devices, drugs, and biologics. This paper will focus

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[12] FDA, *Companion Diagnostics* (Jul. 31, 2014), http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm407297.htm.

[13] *Id.*

[14] Amit Agarwal, Dan Ressler, and Glenn Snyder, *The Current and Future State of Companion Diagnostics*, 8 Pharmacogenomics and Personalized Medicine 99 (2015) (illustrating the potential for companion diagnostics and the various ways companies can develop them under current regulatory and economic obstacles).

[15] FDA, *Paving the Way for Personalized* Medicine, *supra* note 1 at 23.

[16] John Barlow Weiner, *Regulation of Combination Products*, in FDA Regulatory Affairs 361(David Mantus & Douglas J. Pisano Ed., 2014).

[17] FDA, *FDA Approves Emsam (Selegiline) as First Drug Patch for Depression* (Feb. 28, 2006), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108607.htm.

[18] FDA, *Paving the Way for Personalized Medicine*, *supra* note 1 at 10.

[19] *Id.*

[20] *Id.*

on combination products and companion diagnostics and how the FDA regulates them. Part II of this paper will introduce the process that combination products must go through to be allowed on the market, and the FDA's regulatory role in that process. Part III of this paper will analyze the current regulatory regime for companion diagnostics. Part IV will then recommend that the FDA use its experience from regulating combination products and apply a similar regulatory regime for companion diagnostics. Specifically, this paper will recommend that the FDA create an Office of Companion Diagnostics because it will help organize and clarify how companion diagnostics and their corresponding therapeutic products are regulated, and will centralize the necessary expertise to assist in approving these products. With the growth of companion diagnostics, the drug and device regulatory regimes will become more intertwined and interconnected, and this office will help address issues associated with this growing merger. Finally, this paper will conclude by explaining how an Office of Companion Diagnostics will advance personalized medicine by clarifying the regulatory process so industry can focus on the development of companion diagnostics.

I. COMBINATION PRODUCTS

A. History

Because combination products combine components of biological products, drugs, and/or devices, they involve components that would traditionally be regulated under different types of regulatory authorities and different FDA Centers.[21] These centers include the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH).[22] There are three categories of combination products: 1) single-entity combination products (e.g. prefilled syringes, drug-eluting stents); 2) co-packaged combination products (e.g. first aid kits, surgical procedure kits); and 3) cross-labeled combination products (e.g. a drug and a laser that activates it).[23] These products raise regulatory, policy, and review management challenges.[24] Individually, drugs and devices have very distinct regulatory pathways with differing requirements.[25] Drugs must meet stricter safety and efficacy standards, as they achieve their primary purpose by affecting a structure or function of the body.[26] Devices, on the other hand, do not use chemical action either on or within the body

[21] FDA, *About Combination Products*, http://www.fda.gov/CombinationProducts/AboutCombinationProducts/default.htm.

[22] *Id.*

[23] FDA, *Frequently Asked Questions about Combination Products*, http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm.

[24] *Id.*

[25] *See generally* Lewis A. Grossman, *Drugs, Biologics, and Devices: FDA Regulation, Intellectual Property, and Medical Products in the American Health Care System*, in The Oxford Handbook of U.S. Healthcare Law (I. Glenn Cohen et al. ed., 2015) (explaining the law governing drugs, biologics, and devices).

[26] *Id.*

to achieve their intended purpose.[27] Therefore, the statutory requirements for device marketing approval applications are slightly easier to meet.[28]

These differences in regulatory pathways for each component of a combination product can affect all aspects of product development, including pre-clinical testing, clinical investigation, marketing applications[29], manufacturing and quality control, adverse event reporting, promotion and advertising[30], and post-approval modifications[31].[32] In 2002, Congress passed the Medical Device User Fee and Modernization Act (MDUFMA), which required FDA to establish the Office of Combination Products (OCP) and gave the office broad responsibilities covering the regulatory life cycle of drug-device, drug-biologic, and device-biologic combination products.[33] Congress made this requirement because of the challenges of combination products from patient, medical, and legal perspectives.[34]

On December 24, 2002, FDA established OCP and gave it several responsibilities.[35] First, OCP serves as a focal point for combination product issues for agency reviewers and industry.[36] Second, OCP develops guidance and regulations to clarify the regulation of combination products.[37] Third, OCP assigns an FDA center to have primary jurisdiction for review of both combination and single entity (i.e., non-combination) products where the jurisdiction is unclear or in dispute.[38] Fourth, OCP ensures timely and effective premarket review of combination products by overseeing the timeliness of and coordinating reviews involving more than one agency center.[39] Fifth, OCP ensures consistency and appropriateness of post-market regulation of combination products.[40] Sixth, OCP resolves disputes regarding the timeliness of premarket review of

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[27] *Id.*

[28] *Id.* (explaining the differing regulatory requirements for drugs and devices in further detail).

[29] *See* FDA, *Frequently Asked Questions about Combination Products*, *supra* note 23 (explaining that the Office of Combination reviews marketing applications from companies who have developed a product and want FDA approval so they can then legally sell their product to consumers).

[30] The FDA regulates how companies can promote and advertise their products to consumers. The FDA does this to make sure that companies are truthful and don't mislead consumers.

[31] After a product is approved, sometimes new information has been learned and companies sometimes must modify their product. If this occurs, the FDA has certain steps for companies to follow to properly modify their products.

[32] *Id.*

[33] FDA, *Summary of the Medical Device User Fee and Modernization Act of 2002*, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109105.htm.

[34] FDA, *Transcript of Public Hearing on FDA Regulation of Combination Products*, http://www.fda.gov/downloads/CombinationProducts/MeetingsConferencesWorkshops/UCM117123.pdf.

[35] FDA, *Office of Combination Products*, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018184.htm.

[36] *Id.*

[37] *Id.*

[38] *Id.*

[39] *Id.*

[40] *Id.*

combination products.[41] Seventh, OCP updates agreements, guidance documents, and practices specific to the assignment of combination products.[42] Finally, OCP submits annual reports to Congress on the Office's activities and impacts.[43]

B. Assignment

When OCP receives a submission for a combination product to be commercially available in the United States, it designates a center with the primary regulatory responsibility (the "lead")."[44] OCP's decision is based on whether the combination product's "primary mode of action" is as a (1) biologic, (2) device, or (3) drug.[45] "Primary mode of action" (hereinafter referred to as "PMOA") is not defined by statute; the FDA promulgated regulations in 2005 to define the term and address how to determine the PMOA of a combination product.[46] The FDA defines PMOA as the "single mode of action of a combination product that provides the most important therapeutic action of the combination product."[47] The agency defines the most important therapeutic action as the combination product's "mode of action expected to make the greatest contribution to the overall intended therapeutic effects."[48] It defines "therapeutic" effect or action to include any effect or action that is "intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body."[49] Therefore, CBER would likely have the lead for a combination product if it has a biologic PMOA; CDRH if it has a device PMOA; and CDER if it has a drug PMOA.[50]

The FDA determines the PMOA by looking at previously approved products or through case-by-case analysis.[51] For some types of combination products, the constituent part that contributes the PMOA is well established.[52] For example, if the combination product consists of a drug and a device and the device only delivers the drug but does not contribute to the therapeutic effect, the Agency will consistently state that this product's drug is its PMOA.[53] To illustrate, a drug in a prefilled syringe would be considered to provide the PMOA.[54] However, some products require case-by-case analysis because the PMOA can vary among similar combination products. For instance, one drug-device combination product indicated to accelerate wound healing might include a higher strength of a drug

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41 *Id.*

42 *Id.*

43 *Id.*

44 *See* Weiner, *supra* note 16 at 364.

45 *Id.*

46 *See Definition of Primary Mode of Action of a Combination Product*, 70 Fed. Reg. 49,848 (Aug. 25, 2005) (codified at 21 C.F.R. § 3.2 (2005).

47 § 3.2(m).

48 *Id.*

49 §3.2(k).

50 Weiner, *supra* note 16 at 364.

51 *Id.*

52 *Id.*

53 *Id.*

54 *Id.*

than is included in another combination product with the same intended use.[55] The device may provide the PMOA in the combination product that has the weaker drug, while the drug might provide the PMOA in the combination product that includes the stronger drug.[56] Similarly, two combination products that include the same or similar drug and device constituents may have different indications, and the respective contributions of those constituent parts may differ depending on the indication.[57] If possible, the FDA determines the PMOA if, with reasonable certainty, it can determine which constituent part appears to contribute the most to the product's intended therapeutic effects.[58] In some cases, however, where there is not sufficient data available, the FDA uses a two-step algorithm to determine the PMOA and the lead center for the combination product.[59] The first step is to see whether one of the centers is already regulating a combination product that raises similar questions of safety and efficacy.[60] If so, the product is assigned to that center.[61] If not, the second step is to determine which center has the greatest expertise with respect to the most significant questions of safety and efficacy raised by the combination product, and that center will be the lead.[62] In some circumstances, as discussed below, a sponsor may also request a classification or assignment of their product.

C. Request for Designation

If the assignment of a center might be unclear, a sponsor of a combination product may submit a request for designation (RFD) to the OCP for a formal determination.[63] An RFD requests a determination of which FDA center will have primary jurisdiction for premarket review and regulation of a combination product.[64] A product's sponsor must submit an RFD before filing any investigational or marketing application for the product.[65] A RFD includes (1) the identity of the sponsor; (2) a description of the

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[55] *Id.* at 364-65.

[56] *Id.* at 365.

[57] *Id.*

[58] *Id.* The FDA explained: "In general, it would be possible to determine the PMOA of a combination product with 'reasonable certainty' when the PMOA is not in doubt among knowledgeable experts, and can be resolved to an acceptable level in the minds of those experts based on the data and information available to the FDA at the time an assignment is made." *See Definition of Primary Mode of Action of a Combination Product*, *supra* note 46.

[59] *Id.*

[60] *Id.*; *see also* 21 U.S.C.A. § 321(p) (2009) (defining a new drug and explaining that safety and efficacy are determined by experts qualified by scientific training and experience).

[61] Weiner, *supra* note 16 at 365.

[62] *Id.*

[63] 21 C.F.R. § 3.2(j) (2009); *see also* FDA, *RFD Process*, http://www.fda.gov/CombinationProducts/RFDProcess/, 4, (last updated Apr. 15, 2010). A RFD is not necessary for every product. It is recommended when the classification of a product or the FDA center to which it should be assigned is unclear or in dispute.

[64] FDA, *Guidance for Industry: How to Write a Request for Designation (RFD)* 3 (2011), http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM251544.pdf.

[65] *Id.* at 4.

product[66]; and (3) the sponsor's recommendation as to which Agency center should have primary jurisdiction.[67] Within 5 days of receiving a RFD, OCP must review the submission for completeness and determine whether the RFD contains the required information.[68] OCP must then either send the sponsor an acknowledgement letter confirming the filing date of the RFD or notify the sponsor that the RFD was not filed and specify what information is necessary to complete the filing of the RFD.[69] If OCP does not issue a designation letter within 60 calendar days of the filing of the RFD, as required by 21 CFR 3.8(b), the sponsor's recommendation for the classification or assignment of the product will become the designated classification or assignment.[70] If a product sponsor disagrees with the OCP's jurisdictional determination, the sponsor can request reconsideration of a decision within 15 calendar days of receipt of the designation letter.[71] A request for reconsideration cannot exceed 5 pages and cannot include any new information that was not contained in the original RFD.[72] The FDA must then review and give a response to the sponsor within 15 calendar days of receipt of the request for reconsideration.[73] If the sponsor wishes to submit additional or new data, the sponsor must submit a new RFD containing that information, and the OCP will consider that RFD a new submission.[74] It is important to note, however, that the letter of designation issued by the FDA is a binding determination that can only be modified under the conditions outlined in Section 563 of the FD&C Act and 21 CFR 3.9.[75]

D. Regulatory Issues

1. Premarket Regulation: Marketing Authorization Requirements and Processes

A variety of issues arise during the premarket regulation process of combination products. The marketing authorization pathways, regulatory standards, and procedures for combination products are those for drugs, devices, and biological products.[76] However, these pathways, standards, and procedures, having been designed for one type of product, are not always properly applicable to a combination of products. The main issues for combination products concern how to ensure that all of the regulatory

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[66] *See id.* (delineating that a description of the product should include: (a) classification, (b) common or generic name, (c) proprietary name, (d) identification of any component that has either already received premarket approval, is marketed as not being subject to premarket approval, or has received an investigational exemption, (e) chemical, physical, or biological composition, (f) status and brief reports of the results of developmental work, (g) description of the manufacturing processes, (h) proposed use or indications, (i) description of all known modes of action, (j) schedule and duration of use, (k) dose and route of administration of drug or biologic, (l) description of related products, and (m) any other relevant information).

[67] *Id.* at 6-7; *see also* 21 C.F.R. § 3.7(c)(2015).

[68] § 3.8(a).

[69] FDA, *Guidance for Industry: How to Write a Request for Designation (RFD)*, *supra* note 64 at 5.

[70] *Id.*

[71] § 3.8(c).

[72] *Id.*

[73] FDA, *Guidance for Industry: How to Write a Request for Designation (RFD)*, *supra* note 69 at 5.

[74] *Id.*

[75] *Id.* at 3-4.

[76] Weiner, *supra* note 16 at 367.

issues raised by a combination product are appropriately addressed, regardless of the regulatory pathway by which it may enter the FDA.[77] The PMOA standard determines which center will have the lead for regulation of a combination product, however, it does not clear up what types of investigational and marketing authorization submissions should be pursued for the approval of the product.[78] It also does not expressly address what review standards or data requirements should apply for combination products or whether these standards should vary upon which center has the lead.[79] Furthermore, the PMOA standard does not establish how the lead and non-lead centers should coordinate or how sponsors should interact with either.[80] However, statutory language and agency policies, statements, and practice offer insight into these questions.[81] Combination products also pose questions regarding what information is necessary on their investigational applications.

2. Investigational and Marketing Submissions

The FDA only requires one investigational application for a combination product, but a combination product may require more than one marketing application.[82] However, CDER, CBER, and CDRH do not currently have the delegated authority to review all marketing application types.[83] Specifically, CDER has the authority to review some biologics licensing applications (BLAs),[84] new drug applications (NDAs), abbreviated NDAs (ANDAs), and investigational new drug applications (INDs).[85] CDRH has the authority to review Premarket Approvals (PMAs), 510(k)s[86], Humanitarian Device Exceptions (HDEs), and Investigational Device Exemptions (IDEs).[87] Finally, CBER has the authority to review all of these types of submissions.[88] While the FDA has not

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77 *Id.*

78 *Id.* at 367-68.

79 *Id.*

80 *Id.* at 368.

81 Weiner, *supra* note 16 at 368.

82 FDA, *Frequently Asked Questions about Combination Products*, *supra* note 23.

83 Weiner, *supra* note 16 at 368.

84 CDER and CBER both have regulatory responsibility over therapeutic biological products. The categories of therapeutic biological products that CDER regulates are: monoclonal antibodies for in vivo use, most proteins intended for therapeutic use, and immunomodulators. *See* FDA, *Frequently Asked Questions about Therapeutic Biological Products*, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/%20HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm, (last updated Dec. 15, 2014).

85 Weiner, *supra* note 16 at 368.

86 A 510(k) is a premarket notification by a device company to the FDA notifying that the company intends to market a device that is equivalent to another medical device that is already on the market. Essentially, its not a "new" device, and can be more easily classified by the FDA rather than a new device that would require more information. *See* FDA, *510(k) Clearances*, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ (last updated Jan. 26, 2016).

87 Weiner, *supra* note 16 at 368.

88 *Id.*

stated that the submission types associated with the constituent part that provides the PMOA must or may always be used, they usually are.[89]

There are key questions to consider in evaluating what investigational and marketing authorization submissions to make for combination products. First, which constituent part provides the PMOA?[90] Second, which submissions type(s) associated with that constituent part is (are) available for the combination product?[91] Usually, the FDA requires only one marketing application per combination product, particularly if its constituent parts are physically or chemically combined into one product.[92] However, if the FDA permits or requires a marketing authorization for each constituent part, each would be of a type normally associated with that kind of product (e.g. an NDA or ANDA for a drug constituent part; a PMA or 510(k) for a device constituent part).[93] Each submission would be made to the center normally responsible for that type of product (e.g. an NDA would be submitted to CDER and a PMA would be submitted to CDRH).[94] According to the FDA, the centers still coordinate on the review of the product even though each center would receive its own submission to review.[95] The FDA has noted that some of the same data could be presented and relied upon for both marketing authorizations.[96] While the formal submission type may have limited significance for the data needed to support marketing authorization for a combination product, the type of submission(s) available could have other implications relevant to business judgments and product development planning.[97] For example, there is a remarkable difference in user fees for marketing submissions, even though waivers and reduced fees may be available.[98] User fees allow the FDA to collect payments from companies and these fees help the FDA expedite approval processes.[99] Standard fees for NDAs currently range from about $1 million to $2 million, for PMAs being about $250,000, for ANDAs being over $50,000, and for 510(k)s being nearly $5,000.[100] Combination products that are reviewed under a single marketing authorization should be subject to the fee associated with that type of authorization.[101] If two authorizations are necessary, then the fee associated with each applies to the combination product.[102]

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89 *Id.*

90 *Id.* at 361.

91 *Id.* at 368.

92 Suzanne O'Shea, *Working Through the US Rules for Combination Products*, RAJ Pharma 653 (2008).

93 Weiner, *supra* note 16 at 368.

94 *Id.*

95 *Id.*

96 *Id.*

97 *Id.* at 368-69.

98 *Id.*

99 *FDA User Fee Agreements: Strengthening FDA and the Medical Products Industry for the Benefit of Patients: Hearing Before the S. Comm. on Health, Educ., Labor, and Pensions*, 112th Cong. (2012) (statement of Dr. Janet Woodcock, Dir. of CDER at FDA).

100 Weiner, *supra* note 16 at 369.

101 *Id.*

102 *Id.*

Additionally, some marketing submission types offer protections from competition, while others do not. For example, the provisions for marketing a product under a NDA or BLA protect patent rights and grant periods of marketing exclusivity during which the FDA cannot approve follow-on products that seek to rely on the FDA's prior approval of the same or a similar product.[103] However, abbreviated marketing authorizations would be available to allow follow-on applicants to be on the market once such exclusivities expire.[104] In contrast, if a product is marketed under a 510(k), no marketing exclusivity applies, so a follow-on product could be cleared at any time.[105] Finally, if a product is marketed under a PMA, there is a six-year data exclusivity provision.[106] Aside from regulatory pathways and marketing applications, combination products must also meet substantive requirements.

3. Standards for Marketing Authorization

While the FDA has not published general guidance on what substantive requirements must be met to obtain marketing authorization for a combination product, it has stated that each constituent part of a combination product retains its legal status as a drug, device, or biologic.[107] In specific guidance for products, the FDA has indicated that considerations raised by each constituent part will be addressed in keeping with standard approaches for such products.[108] For example, considerations normally reviewed for an injector marketed under a device pathway would also be considered for an injector being reviewed under a NDA or BLA.[109] The FDA has also indicated a marketing authorization for a combination product must address questions associated with each of its constituent parts, as if each part were marketed independently.[110] Furthermore, the FDA has indicated that a marketing authorization must also consider questions of safety and efficacy that arise when constituent parts are combined.[111] To meet these requirements, experts from several offices must work together to evaluate the combination product.

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[103] *See* 21 C.F.R. § 314.108 (2015) (explaining that marketing exclusivities were designed to promote a balance between a new drug innovation and generic drug competition).

[104] *Id.*

[105] Weiner, *supra* note 16 at 369.

[106] 21 U.S.C. § 360(j)(h)(4)(A) (explaining that any information contained in an application for premarket approval will not be publicly available for six years).

[107] Weiner, *supra* note 16 at 369.

[108] *Id.*

[109] *See, e.g.,* FDA, *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* (2009), http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf; FDA, *Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4 (Draft)* (2013), http://www.fda.gov/RegulatoryInformation/Guidances/UCM122047.html.

[110] *See* FDA, *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*, *supra* 109.

[111] *Id.*

4. Inter-Center Coordination and Sponsor-FDA Interaction For Premarket Review of Combination Products

The FDA has established standard operating procedures (SOPs) and mechanisms to facilitate inter-center coordination, agency-sponsor interaction, and coordination between sponsors and third parties.[112] Combination products often require complex inter-center coordination and interaction in order to facilitate premarket review.[113]

Premarket review systems for combination products provide for coordination between the lead center and the center(s) that typically regulate the other constituent part(s) included in the combination product.[114] For example, the FDA has an SOP that includes a formalized process for enabling the lead center to seek input from the secondary center(s).[115] OCP sends annual reports to Congress and these include data tracking of the number of consults between centers.[116]

Sponsors coordinate with the FDA through the lead center.[117] A product's sponsor can work with the lead center to confirm that other centers, offices, and staff are participating in meetings and reviewing the sponsor's submission in a timely manner.[118] OCP facilitates scheduling of meetings and coordinates other matters between the sponsor and the FDA.[119] Furthermore, OCP helps resolve disputes regarding product review.[120]

Good relationships between sponsors and manufacturers of different types of products can further support product review and the approval process.[121] For example, if a drug sponsor and a device manufacturer are developing a product together, their relationship can benefit the approval process.[122] If they have a good relationship, they will be better equipped to work together and address any concerns the FDA centers may have. Furthermore, if a device manufacturer already has an approved independent product that is similar to the one they are developing with a drug sponsor, the device manufacturer can allow the FDA to access the data for the already approved device.[123] If the FDA can look at a previous approval and the data and information associated with that approval, the FDA's decision process for a new product that is similar will be easier and likely expedited. Once a combination product is approved, OCP's role does not end.

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112 Weiner, *supra* note 16 at 370.

113 *Id.*

114 *Id.* at 370-71.

115 *Id.*

116 *Id.* at 371.

117 *Id.* at 370-71.

118 *Id.* at 371.

119 *Id.* Note that a product's sponsor and its lead center are not required to meet. However, if a product's sponsor requests a meeting with its lead center, OCP schedules the meeting. As OCP is the focal point for combination products, it handles logistical planning so experts can focus on the combination product itself.

120 *Id.*

121 *Id.*

122 *Id.* at 370-71.

123 *Id.*

E. Post-Market Regulation

The OCP's responsibilities include ensuring consistent and appropriate post-market regulation of combination products.[124] To that end, OCP has issued a final rule on current good manufacturing practices (cGMPs), a proposed rule on post-marketing safety reporting (PSR) for combination products, and a final rule on unique identification for devices.[125] With each of these, OCP has worked to streamline compliance with regulatory requirements while simultaneously ensuring that sponsors demonstrate the safety and effectiveness of combination products.[126] When OCP developed the cGMP and PSR rules for combination products, OCP worked with expert staff from the various centers to review the applicable regulations for drugs, devices, and biological products.[127] OCP aimed to ensure that these regulatory requirements were met and to minimize any unnecessary overlap.[128]

Combination products require coordination across centers and other agency offices during post-market regulatory activity.[129] The different Centers and the Office of Regulatory Affairs can work together on manufacturing facility inspection activities and on evaluation and response to post-market safety reports.[130] OCP assists in that coordination so that combination products are in compliance with all regulatory requirements and can maintain their presence on the market.[131]

F. Disputes over the OCP's Center Assignment

Generally, OCP has worked well with combination product sponsors; however, one case, *Prevor v. FDA*,[132] has garnered a great deal of attention and has highlighted several issues associated with combination products. After developing its drug-device combination product, Diphoterine Skin Wash (DSW), Prevor requested that the FDA assign CDRH as its lead center.[133] Prevor argued that the product's PMOA came from its device constituent part.[134] However, the FDA stated that DSW had a drug PMOA, and Prevor challenged this determination.[135]

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[124] Mark D. Kramer, *FDA'S Office of Combination Products: Roles, Progress & Challenges* 3 http://www.fda.gov/downloads/CombinationProducts/MeetingsConferencesWorkshops/UCM116739.pdf.

[125] Weiner, *supra* note 16 at 372.

[126] *Id.*

[127] *Id.*

[128] *Id.* OCP has been mostly successful in its endeavors and has not had many disputes. However, there have been some, which will be discussed later on in this article.

[129] *Id.* at 372-73.

[130] *Id.*

[131] *Id.* at 373.

[132] 895 F. Supp. 2d 90 (D.D.C. 2012) (holding that the FDA failed to articulate why it loosened guidelines in guidance document allowing for combination product designation if a primary purpose of a product is achieved "even in part" by chemical action).

[133] *Id.* at 94.

[134] *Id.*

[135] *Id.* (stating that the liquid does not meet the definition of device but does, however, meet the definition of drug at 21 U.S.C. § 321(g))

In its challenge, Prevor focused on the original intention of DSW. Prevor created DSW to mitigate chemical burns.[136] It is a liquid substance that is contained in a canister propelled by pressurized gas.[137] The liquid substance is colorless and odorless and is 96% water and 4% diphoterine.[138] Prevor claimed that the "first use is a physical/mechanical mode of action (comprises approximately 90% of DSW's overall effect), while the second one is a chemical mode of action (comprises 10% of DSW's overall effect)."[139] The FDA stated that if the product depends "at least in part" on any chemical action, then it is automatically not a device.[140] Prevor countered this argument claiming that OCP erred by "contradicting established agency precedents, disregarding information provided in the RFD, and applying a novel review standard not found in or supported by law or regulation."[141] Specifically, Prevor claimed that the FDA incorrectly applied the FDCA's definition of a device.[142] According to the statute, a product is not a device if it "achieves its primary intended purposes through chemical action within or on the body of man."[143] Prevor disagreed with the FDA's conclusion that DSW has more than one *primary* intended purpose.[144] Specifically, Prevor stated that the neutralization of chemicals is not one of DSW's primary intended purposes.[145]

The district court agreed with Prevor and said that the FDA's interpretation improperly allowed "at least in part" or "even in part" to expand the meaning of "primary."[146] The court stated that (1) the FDA treated any purpose of DSW as a primary intended purpose, and (2) the FDA treated achievement even in part of any purpose through chemical action as achievement of a primary intended purpose through chemical action.[147] The court remanded the case to allow the agency to make a determination consistent with the holdings in its opinion.[148]

On remand, the FDA reached the same conclusion that DSW was a drug, yet with one difference.[149] The FDA found that DSW had only one primary purpose: "to help prevent and minimize accidental chemical burn injuries."[150] Prevor argued against a

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136 *Id.* at 92.

137 *Id.*

138 *Id.*

139 *Id.*

140 *Id.* at 94.

141 *Id.*

142 *Id.*

143 *Id.* at 97 (citing 21 U.S.C. § 321(h)).

144 *Id.*

145 *Id.*

146 *Id.* at 98 (stating that "Inasmuch as the statute seeks to identify *primary* intended purposes that are achieved through chemical action, it would be magnificently expanded if a *primary* purpose could automatically be achieved "at least in part" or "even in part" by chemical action. Primary means principal, first among others, foundational.")

147 *Id.* at 100-101.

148 *Id.* at 101.

149 67 F. Supp. 3d 125, 125 (D.D.C.2014).

150 *Id.* at 131.

second remand back to the FDA.[151] Instead, Prevor asked the court to classify DSW as a medical device or as a combination product with a medical device as the primary mode of action.[152] Prevor and the FDA both filed Motions for Summary Judgment.[153]

On September 9, 2014, the U.S. District Court for the District of Columbia rejected Prevor's argument and denied the FDA's motion.[154] The court held that in selecting one primary purpose alone, the FDA conveniently avoided distinguishing between primary and secondary purposes.[155] Furthermore, the court referred to the statute saying that a product does not meet the device definition if it "achieves its primary intended purposes through chemical action within or on the body."[156] The court implied that the FDA's definition of "achieve" as "chemical action [that] meaningfully contributes to its primary intended purpose" was creative.[157] Unlike the FDA, the court did not find that "achieve" means "meaningfully contribute."[158] In ruling against the FDA, the court emphasized, "Chemical action that helps or plays a significant part in bringing about a specific result is more than *de minimis* involvement, but it does not fulfill the congressional directive that the chemical action must achieve, i.e., accomplish or attain, the primary purpose."[159] Furthermore, the court held that the FDA's "meaningfully contribute" language appeared to be a "significant shift" in the agency's practices when classifying products.[160] The court noted that this language does not appear in legislative history, any FDA guidelines, or in any other classification decisions.[161] While the FDA is allowed to adopt new approaches, it must offer a reasonable analysis for its new approach.[162] In this case, the FDA did not offer such analysis and the court stated that "an agency interpretation of a relevant provision which conflicts with the agency's earlier interpretation is 'entitled to considerably less deference' than a consistently held agency view."[163] The court acknowledged that agency determinations are usually regarded with deference, particularly one such as this where the FDA has made a scientific finding in its area of expertise.[164] Moreover, the court recognized that on remand, the FDA could again find a drug primary mode of action as long as it also adopts a "plausible

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[151] *Id.* at 139 (suggesting that the FDA had already reviewed the record for a second time, and would likely not change its decision).

[152] *Id.* at 139.

[153] *Id.* at 128.

[154] *Id.; see also* Gail Javitt, *Cases to Watch in 2014: Prevor v. FDA (Prevor II)*, Sidley Austin, *available at* http://www.fdli.org/docs/medical-devices/javitt.pdf?sfvrsn=0.

[155] 67 F. Supp. 3d at 134.

[156] *Id.* at 136.

[157] *Id.* (suggesting that the FDA was trying to improperly mold the definition of achieve).

[158] *Id.* (referencing the dictionary and clarifying that "achieve" means "to carry out successfully," while "contribute" implies a lesser involvement and only helps something happen.)

[159] *Id.* at 136-137.

[160] *Id.* at 138.

[161] *Id.*

[162] *Id.*

[163] *Id.* (quoting *I.N.S. v. Cardoza-Fonseca*, 480 U.S. 421, 448 n. 30 (1987)).

[164] *Id.* at 139.

construction of the relevant statutory language."[165] However, the court found that the record showed that FDA's classification decision was based on an "erroneous and unreasonable interpretation of the law."[166] For these reasons, the court remanded the case back to the FDA for further proceedings consistent with its opinion.[167]

This case highlighted critical gaps in the regulation of combination products. First, the FDA's interpretation of "primary" in the PMOA standard was vague because PMOA has not been statutorily defined. While OCP has been able to work through most disputes or disagreements, *Prevor* demonstrated that the industry may benefit from further insight into the FDA's thought process in interpreting a PMOA.[168] Second, the FDA's interpretation of chemical action under Section 201(h) of FDCA is unclear and also warrants further insight.[169] Still, despite the potential benefits of more guidance, the industry already benefits from the OCP.

G. Benefits of OCP

Despite *Prevor*, OCP has evidently been a success. For an office that holds such an incredible amount of responsibility, it has had very few disputes. Furthermore, industry describes the OCP as a "blessing."[170] The Combination Products Coalition (CPC)[171] states that since its establishment, the OCP has served as an important resource to manufacturers.[172] CPC states that OCP "consistently helps manufacturers navigate the murky and sometimes stormy waters created by the cross-center regulation of their products."[173] Most notably, CPC praises OCP for "get[ting] some of the highest marks of any office at FDA when it comes to responding quickly to pleas for help."[174] CPC further recognizes OCP's role in developing guidance documents regarding the development of combination products and believes OCP to be an "extremely valuable resource."[175] CPC acknowledges that there are areas where OCP can improve, but it is happy that OCP is at the FDA to manage issues regarding combination products.[176] CPC has stated that OCP can improve by: 1) clarifying the roles and responsibilities of OCP vis-à-vis the various centers; 2) updating the intercenter agreements; 3) developing guidance on human

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165 *Id.*

166 *Id.* (citing *Chevron v. Natural Resources Defense Council*, 467 U.S. 837, 843, n. 9 (1984)) ("The judiciary is the final authority on issues of statutory construction and must reject administrative constructions which are contrary to clear congressional intent.").

167 *Id.* at 128.

168 *Id.* at 134.

169 21 U.S.C. § 321(h) (2015).

170 *Op Ed: Counting Our Blessings with the Office of Combination Products*, Combination Products Coalition (May 1, 2013), http://combinationproducts.com/news/#post-613.

171 *What is the CPC?,* Combination Products Coalition, http://combinationproducts.com/about/ (identifying itself as "a group of leading companies in the drug, device and biologics industries [that] works to improve the regulatory environment for combination products by developing and advocating policy positions on regulatory issues affecting combination products").

172 Combination Products Coalition, *Op Ed*, *supra* note 170.

173 *Id.*

174 *Id.*

175 *Id.*

176 *Id.*

factors and usability testing for combination products; 4) tackling the unique issues associated with conducting clinical trials on combination products; and 5) enhancing transparency through publication of Request for Designation letters. While OCP can improve in some ways, it has overall been a positive development.[177] CPC remembers the regulation of combination products before OCP existed and believes the industry is "lucky" to have OCP.[178] As combination products have benefited from OCP, companion diagnostics could benefit from a comparable office.

H. Companion Diagnostics

As stated earlier, companion diagnostics are medical devices, often in vitro devices, which provide information that is essential for safe and effective use of a corresponding drug or biologic.[179] The devices test to see whether a drug or biologic's benefits outweigh its risks for a particular patient.[180] The area of companion diagnostics began when the FDA approved Herceptin, a cancer drug that shuts off a protein present in abnormally high amounts in about one-quarter to one-third of aggressive breast cancers.[181] The companion diagnostic test looks for excessive levels or extra copies of the protein HER2 in a patient's tumor, because this indicates that Herceptin could be an effective treatment for that patient.[182] At the time of this article's publication, only about twenty companion diagnostics have been approved.[183] These new technologies are making it increasingly possible to individualize, or personalize, medical therapy.

Currently, there is no Office of Companion Diagnostics at the FDA, but there is an Office of In Vitro Diagnostics and Radiological Health (OIR).[184] OIR is comprised of the Office of the Director, which includes the personalized medicine staff and seven divisions.[185] This office handles several tasks including: 1) regulating in home and laboratory diagnostic tests, 2) regulating radiological medical devices, 3) regulating radiation-emitting non-medical products, and 4) implementing the Mammography Quality Program authorized by the Federal Mammography Quality Standards Act of 1992.[186] To foster innovation,

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177 *Id.*

178 *Id.*

179 FDA, *Companion Diagnostics*, http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm407297.htm.

180 *Id.*

181 FDA, *Personalized Medicine and Companion Diagnostics Go Hand-in-Hand*, http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm407328.htm.

182 *Id.*

183 FDA, *List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)*, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.

184 FDA, *Office of In Vitro Diagnostics and Radiological Health*, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm115904.htm.

185 *Id.* These divisions are: Division of Chemistry and Toxicology Devices (DCTD), Division of Immunology and Hematology Devices (DIHD), Division of Microbiology Devices (DMD), Division of Radiological Health (DRH), Division of Mammography and Quality Standards (DMQS), Division of Molecular Genetics and Pathology (DMGP), Division of Program Operations and Management (DPOM).

186 *Id.*

OIR combines pre-market and post-market responsibilities into one multi-disciplinary office.[187] Additionally, OIR administers the federal Clinical Laboratory Improvement Amendments (CLIA).[188] This can be a tremendous undertaking because it can be unclear as to which division handles companion diagnostics, particularly because companion diagnostics fall under the expertise of so many of these divisions. Compounding this problem is the fact that the regulatory regime for companion diagnostics is murky. Furthermore, there is no office that links CDRH to either CBER or CDER when regulatory issues regarding companion diagnostics arise. As discussed below, the FDA issued guidance for industry and FDA staff for in vitro companion diagnostic devices on August 6, 2014, but failed to resolve certain questions.[189]

I. Guidance for In Vitro Companion Diagnostic Devices

The guidance issued by the FDA for in vitro companion diagnostic devices helped the industry, but left many unanswered questions.[190] The guidance assisted (1) sponsors planning to develop a therapeutic product requiring the use of an in vitro companion diagnostic device for the therapeutic product's safe and effective use, and (2) sponsors planning to develop an in vitro companion diagnostic device intended to be used with a corresponding therapeutic product.[191] The guidance addressed several concerns associated with in vitro companion diagnostic products. Specifically, inadequate performance of a companion diagnostic could lead to withholding appropriate therapy, or administering inappropriate therapy.[192] Therefore, to address the remaining questions regarding safety and effectiveness of both companion diagnostics and their complementary therapeutic product, the FDA assesses these products through premarket review and clearance.[193] In the guidance document, the FDA stated that its aim was to clarify relevant policies for industry, develop internal procedures, and ensure effective communication between relevant centers. Furthermore, FDA aimed to promote consistent advice, efficient development, coordinated product review. [194]

The FDA noted its expectation that most therapeutic product and In Vitro Companion Diagnostic Devices (IVD) pairs will not meet the definition of combination product under 21 CFR 3.2(e).[195] This is because the FDA stated that it intends to require separate marketing applications for a therapeutic product and a companion diagnostic device,

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187 *Id.*

188 *Id.* CLIA regulates laboratory testing and requires clinical laboratories to be certified by their state as well as the Center for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing. For further explanation of CLIA, *see* FDA, *Clinical Laboratory Improvement Amendments (CLIA)*, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm.

189 FDA, *In Vitro Companion Diagnostic Devices* (Aug. 6, 2014), available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf.

190 *Id.*

191 *Id.* at 4.

192 *Id.* at 6.

193 *Id.*

194 *Id.*

195 *Id.* at 6 n. 5.

regardless of whether the products could constitute a combination product.[196] However, the FDA stated that the standards for review, approval or clearance would be the same.[197]

1. Timeline

The FDA stated that ideally, a therapeutic product and its companion diagnostic will be developed and cleared contemporaneously.[198] However, the FDA recognized that there may be cases when contemporaneous development is not possible.[199] A companion diagnostic could be a new device, a new version of an existing device, or an existing device that has already been approved for another purpose.[200]

2. Review And Approval

In the guidance document, the FDA said that it reviews companion diagnostics and therapeutic products under applicable regulatory requirements.[201] In other words, the FDA reviews companion diagnostics under the device authorities of the Federal Food, Drug, and Cosmetic (FD&C) Act, and therapeutic products under section 505 (drug products) of the FD&C Act or section 351 (biological products) of the Public Health Service Act.[202] The FDA aims to review each companion diagnostic device application within the context of its corresponding therapeutic product.[203] The FDC stated that when a new therapeutic product requires a companion diagnostic to be safe and effective use, the two products should be developed and approved contemporaneously.[204] Before approving a therapeutic product, the FDA will make sure that the companion diagnostic device meets the applicable standard for safety and effectiveness.[205] Furthermore, the FDA stated that it will generally not approve a therapeutic product if the companion diagnostic device is not approved or cleared for the same indication.[206]

Later in the guidance, the FDA acknowledged that there are two situations where it may approve a therapeutic product even if its companion diagnostic device has not yet been approved.[207] The FDA noted that in such situations, it expects that the companion diagnostic device will be subsequently approved.[208] First, the FDA stated that it may approve a new therapeutic product intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists, even if the therapeutic product's companion diagnostic has not been approved, if the FDA concludes that the

196 *Id.*; *see also* 21 C.F.R. § 3.4(c) (2015).

197 FDA, *In Vitro Companion Diagnostic Devices*, *supra* note 189.

198 *Id.* at 7.

199 *Id.*

200 *Id.*

201 *Id.*

202 *Id.*

203 *Id.*

204 *Id.*

205 *Id.*

206 *Id.*

207 *Id.* at 9.

208 *Id.*

benefits outweigh the risks.[209] Second, the FDA might identify a serious safety issue and require revised labeling for an already approved therapeutic product, even if the companion diagnostic device has not yet been approved.[210] In this second scenario, the FDA will similarly compare the possible benefits of the therapeutic product against the possible risks of an unapproved companion diagnostic device.[211] If the benefits outweigh the risks, the FDA will not delay approval of changes to the labeling of the therapeutic product until the companion diagnostic device is approved or cleared.[212] The FDA emphasized that it generally will determine that a serious safety issue exists before approving a supplement to an approved therapeutic product application.[213] In addition to the review and approval process, there are other policies that FDA and industry alike must keep in mind.

3. General Policies

If a therapeutic product requires the use of a companion diagnostic for its safe and effective use, an approved companion diagnostic should be available for use once the therapeutic product is approved.[214] The FDA has stated that it will apply a risk-based approach to determine the regulatory pathway for companion diagnostic devices, as it does with all medical devices.[215] The regulatory pathway will depend on the level of risk to patients based on the intended use of the device and the controls necessary to assure safety and efficacy.[216] Therefore, the level of risk will establish whether a companion diagnostic requires a PMA or a 510(k).[217]

After completing review of the applications for a therapeutic product and a companion diagnostic, the FDA has stated its intention to issue approvals for both products at the same time.[218]

If a diagnostic device is already legally marketed and its manufacturer intends to market its device for a new use as companion diagnostic with a therapeutic product, the FDA would likely consider this a new use for the device and would require an additional premarket submission.[219]

New companion diagnostic devices intended to be used in the same manner as an existing approved companion diagnostic device will be reviewed under a PMA or a traditional 510(k) as appropriate.[220] Although this guidance gives industry some insight into the FDA's processes, industry is still unable to find answers to all of its questions.

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209 *Id.*

210 *Id.*

211 *Id.*

212 *Id.*

213 *Id.*

214 *Id.*

215 *Id.* at 10.

216 *Id.*

217 *Id.*

218 *Id.* at 10.

219 *Id.*; *see also* 21 C.F.R. §§ 807.81(a)(3)(ii), 814.39(a).

220 FDA, *In Vitro Companion Diagnostic Devices*, *supra* note 189 at 10.

4. Unanswered Questions and Problems with the Guidance

While the guidance document for companion diagnostics addressed many concerns regarding companion diagnostic products, there are still many critical gaps that make it difficult for products to enter the market. First, there are very different timelines associated with the development of drugs and biologics versus diagnostics, and the general concurrent approval requirement detailed in the guidance adds a significant amount of time required for the commercialization of products.[221] Furthermore, the FDA stated in the guidance that it wants a companion diagnostic to be approved before the drug it is being paired with, but has stated that under some circumstances, it will allow a drug to be approved first.[222] While industry says that this apparent flexibility on the FDA's part can be helpful, it would be more effective and beneficial to have specific guidance on how to avoid a delayed companion diagnostic approval.[223]

Second, if there are issues regarding the co-development of drugs and companion diagnostics, the FDA has simply offered to meet with the products' sponsors, but has not issued specific advice.[224] While such a case-by-case analysis works now, as more companion diagnostic and therapeutic product pairs are developed, a case-by-case method may not be sustainable. Industry can benefit from further guidance specifically on co-development of drugs, biologics, and devices.[225] This would allow companion diagnostics and their corresponding therapeutic products to be developed more quickly, which would benefit all stakeholders.[226]

II. RECOMMENDATION

Companion diagnostics bring up similar issues that combination products did before there was an OCP: Inter-center coordination, FDA and sponsor interaction, multiple marketing applications, disputes between centers and with sponsors, and long and delayed approval processes.[227] While OCP has not yet resolved certain issues, it has been tremendously helpful to the world of combination products.[228] Therefore, the creation of an Office of Companion Diagnostics would similarly advance the development of those products.

The Office of Companion Diagnostics can help with all of the issues that the FDA and industry struggled with before there was an Office of Combination Products.[229] While

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[221] Richard Park, *Assessing FDA's Final Guidance on Companion Diagnostics*, Medical Design Technology (Aug. 22, 2014), http://www.mdtmag.com/blogs/2014/08/assessing-fda%E2%80%99s-final-guidance-companion-diagnostics.

[222] *Id.*

[223] *Id.*

[224] *Id.*

[225] *Id.*

[226] *Id.*

[227] Combination Products Coalition, Op Ed, *supra* note 170. As companion diagnostics work with their corresponding therapeutics, they require the expertise of multiple offices and Centers at FDA. Therefore, an office that can be a focal point and coordinate the necessary experts and knowledge can streamline the approval process for companion diagnostics.

[228] *Id.*

[229] *Id.*

the FDA already has the expertise within its centers to help companion diagnostics and their corresponding therapeutic products be approved for the market, the FDA needs to centralize this expertise in an office where staff members can delegate responsibilities, help guide sponsors, keep track of where products are in the regulatory process, and help resolve disputes.[230] An Office of Companion Diagnostics can help streamline the approval process for companion diagnostics, thereby encouraging innovation and furthering personalized medicine.

A. Congress's Role

For an Office of Companion Diagnostics to become a reality, Congress must take several steps. First, Congress must mandate that FDA create an Office of Companion Diagnostics through a statute that would amend the FDCA, similar to the MDUFMA establishing the OCP in 2002.[231] This office should be authorized to set the standard of review for companion diagnostics and coordinate the various FDA centers reviewing marketing applications. Giving the Office of Companion Diagnostics this authority would encourage the efficient use of FDA resources, increase expertise within FDA's staff, and establish accountability for the agency's actions regarding marketing applications. Considering that an Office of Companion Diagnostics would be experimental, Congress should include a period of time to measure the success of the office. If at the end of this period, the office proves unsuccessful, the mandate should "sunset," eliminating the office. Congress should also review the office on an annual basis, just like it does with OCP.[232]

Before an Office of Companion Diagnostics can be created, the Congressional Budget Office (CBO) will need to analyze how much money such an office would cost.[233] The CBO report will likely include an estimate of how much the office will cost over a period of time, at which point provisions would sunset if unsuccessful.[234] The CBO will recommend a certain amount of Congressional appropriations necessary for the office.[235] It is important to note that the Office of Companion Diagnostics will likely be more expensive in its first year than following years because more staff will be necessary for updating product tracking and establishing operating procedures for the office.[236]

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230 Combination Products Coalition, Op Ed, *supra* note 170.

231 H.R. Rep. No. 107-728(II) (2002).

232 FDA, *Combination Products: Annual Reports to Congress*, (Oct. 30, 2015), http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118402.htm.

233 H.R. Rep. No. 107-728(II) (stating the information in the CBO report was prepared prior to the creation of the Office of Combination Products). It is normal practice for the CBO to determine how much money a new office will cost and let Congress know so that Congress can use that amount when voting and passing appropriations bills.

234 *Id.*

235 *Id.*

236 *Id.*

1. User Fees

The Office of Companion Diagnostics could be funded partially by appropriations from Congress and partially by fees paid by the products' sponsors.[237] As industry will benefit from streamlined approval it is appropriate that they pay the normal user fees for their therapeutic products and the corresponding companion diagnostics, as well as an additional fee. These fees would fund the Office of Companion Diagnostics and go to processing the separate marketing applications for the therapeutic product and the companion diagnostic.[238] Congress may anticipate that industry will not want to pay an additional user fee, and provide for various user fee waivers, like those available under MDUFMA and the Prescription Drug User Fee Act (PDUFA).[239]

MDUFMA provides more limited user fee waiver options than PDUFA provides.[240] Under MDUFMA, almost every sponsor must pay the same standard fee upon submitting a device application.[241] However, a small business, i.e., one whose annual gross sales and revenues is less than or equal to $30 million, follows a different fee structure.[242] A small business pays 38% of the standard PMA and BLA fee and 80% of the standard 501(k) fee.[243] MDUFMA also provides a one-time waiver for the first premarket application from a qualified small business.[244] As MDUFMA applies to combination products, it would likewise apply to companion diagnostics.[245]

PDUFA offers more options for user fee waivers.[246] PDUFA offers a waiver for the first human drug application from a small business.[247] However, PDUFA defines a small business differently than MDUFMA.[248] Under PDUFA, a small business is one that has fewer than 500 employees for its business and affiliates.[249] PDUFA also offers waivers: 1) when necessary to protect the public health; 2) when the fee would present a significant barrier to innovation because of the applicant's limited resources or other circumstances; and 3) the fees would exceed the Secretary's anticipated present and future costs of reviewing the applicant's human drug applications.[250] Furthermore,

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237 *Id.*

238 *Id.*

239 *See* FDA, *Guidance for Industry and FDA Staff: Application User Fees for Combination Products* (2005), http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147118.pdf (discussing the various user fee waivers under PDUFA and MDUFMA for combination products).

240 *Id.*

241 *Id.*

242 *Id.*

243 *Id.*

244 *Id.*

245 *Id.*

246 *Id.* at 6.

247 *Id.*

248 *Id.*

249 *Id.*

250 *Id.* at 6; *see also* FDA, *Guidance for Industry: User Fee Waivers, Reductions, and Refunds for Drugs and Biological Products* (2011) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079298.pdf; FDA, *Guidance for*

PDUFA applications that do not require clinical data for approval only require half the fee that is necessary for applications that do require clinical data for approval.[251] Similarly, NDA or BLA supplements that require clinical data for approval are also assessed half the full application fee; whereas, NDA or BLA supplements that do not require clinical data are not assessed a fee.[252]

As companion diagnostics and their therapeutic products are becoming increasingly innovative and furthering personalized medicine, the PDUFA barrier to innovation waiver will likely apply to them. This waiver applies to innovative combination products for which two applications are appropriate.[253] The FDA believes that "combination products may incorporate cutting edge, innovative technologies that hold great promise for advancing patient care."[254] Furthermore, the FDA considers that combination products will make treatment safer or more effective.[255] This closely parallels companion diagnostics and their corresponding therapeutic products, which will personalize care for each patient.[256] The FDA recognizes that the assessment of two marketing application fees for an innovative combination product could represent a significant barrier to its development.[257] The PDUFA barrier to innovation waiver allows the FDA to reduce the additional fee burden for innovative combination products when the person or company has limited resources.[258] Similarly, companion diagnostics and their corresponding therapeutic products could benefit from the barrier to innovation waiver.

The FDA cites several factors that it considers in determining product eligibility for an "Innovative Combination Product" waiver, which are likewise applicable to companion diagnostics. First, the product must address an unmet medical need in the treatment, diagnosis or prevention of disease.[259] It can do this in areas where there is no approved alternative treatment or means of diagnosis, or if the companion diagnostic offers "significant, meaningful advantages" over existing approved alternative treatments.[260] Such advantages may include demonstrated superiority over existing treatments, ability to provide clinical benefit for those patients unable to tolerate current treatments, ability to provide clinical benefit without the serious side effects associated with current treatments, providing greater convenience or ease of use for patients and/or healthcare providers, improving safety by resulting in fewer adverse events, or improving

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Industry: Fees-Exceed-The-Costs Waivers Under the Prescription Drug User Fee Act (1999) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079305.pdf.

[251] FDA, *Guidance for Industry and FDA Staff: Application User Fees for Combination Products*, *supra* note 239 at 6.

[252] *Id.*

[253] *Id.*

[254] *Id.* at 7.

[255] *Id.*

[256] FDA, *Companion Diagnostics*, *supra* note 12.

[257] FDA, *Guidance for Industry and FDA Staff: Application User Fees for Combination Products*, *supra* note 239.

[258] *Id.*

[259] *Id.* at 8.

[260] *Id.*

effectiveness by providing better patient compliance.[261] Second, the FDA also considers if one of the two applications includes a new molecular entity, has been designated as a priority drug or is eligible for expedited device review, or has been granted fast track status.[262] The FDA notes that the existence of a treatment alternative would weigh against deciding that a product is innovative.[263]

As the market for companion diagnostics is projected to grow at a substantial rate, sponsors face challenges. For instance, some therapeutic product sponsors may not have the expertise to develop a companion diagnostic. Independent developers may view companion diagnostics as a high-risk investment because its success would be linked to the regulatory approval of its corresponding therapeutic product.[264] However, on the other hand, companion diagnostics may allow for optimal patient selection for a given therapeutic product which would increase the chances that an investigational product will show substantial evidence of safety and efficacy and make it more likely that the novel therapeutic will obtain FDA approval.[265] Congress should consider these challenges and potential benefits, and create a special waiver for companion diagnostics like the Innovative Combination Product Waiver.[266] This could reassure sponsors, encourage innovation, and result in specific, targeted therapies that can help a larger number of patients.

2. Incentives

Companion diagnostics not only pose great potential benefits for product sponsors, they also pose great risk in their investment. Companion diagnostics and their therapeutic products are dependent upon each other for approval and success, making the regulatory hurdles even greater.[267] Considering these risks, manufacturers may not want to invest money into research and development for two products. However, the benefits of precision medicine for patients are great, and Congress should encourage innovation of companion diagnostics. One option is for Congress to extend the market exclusivity for drugs that rely on companion diagnostics.[268] Another option is to give companion diagnostics and their therapeutic products priority or accelerated review.[269] This paper will not go into the logistics of these options, but they are worthy of Congressional consideration.

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[261] *Id.* at 8-9.

[262] *Id.* at 9.

[263] *Id.*

[264] Vern Noviel et al., *The Rise Of Companion Diagnostics In Personalized Medicine*, Law360 (Jun 5, 2015), http://www.law360.com/articles/664258/the-rise-of-companion-diagnostics-in-personalized-medicine.

[265] *Id.*

[266] FDA, *Guidance for Industry and FDA Staff: Application User Fees for Combination Products*, *supra* note 239 at 6-9.

[267] FDA, *In Vitro Companion Diagnostic Devices*, *supra* note 189 at 8.

[268] *See Response to Request for Information on the Strategy for American Innovation Report*, National Health Council 3-5 (Sept. 23, 2014), http://www.nationalhealthcouncil.org/sites/default/files/NHCcommentstoStrategyforAmericanInnovationRFI.pdf.

[269] *See* FDA, *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review* (Sept. 14, 2015), http://www.fda.gov/ForPatients/Approvals/Fast/default.htm.

B. Differences between OCD and OCP

While the Office of Combination Products provides a template for an Office of Companion Diagnostics, companion diagnostics and their corresponding therapeutic products are different and will require a different process from combination products. First, an Office of Companion Diagnostics will need to issue a guidance document on substantive requirements for marketing authorization, which will help industry in their applications.[270] The FDA will also likely need to pursue notice and comment rulemaking pursuant to the Administrative Procedure Act to avoid product sponsors alleging arbitrary and capricious action.[271]

Second, experts from CBER or CDER and CDRH should meet to discuss the data that is submitted with each application for each product.[272] As companion diagnostics will determine how best to administer their corresponding products, there will be some overlap of data submitted with their applications.[273] Experts from the different FDA centers will need to discuss this overlap of data as well as issues of safety and efficacy that arise when the companion diagnostic is used with its therapeutic product.[274] Additionally, unlike combination products, there will be no lead center for the approval process of the companion diagnostic and its therapeutic product. Thus, an Office of Companion Diagnostic should create an SOP to facilitate inter-center coordination, as companion products may require more coordination to streamline the regulatory process.

Third, an Office of Companion Diagnostics will need to create an SOP to address what happens when a drug and device are not cleared contemporaneously. Currently, there is uncertainty about this, which needs to be addressed as manufacturers have marketing and business development concerns.

Fourth, if a companion diagnostic might have a delayed approval, there needs to be an SOP that revises the regulatory timeline and notifies the product sponsor.

Fifth, an Office of Companion Diagnostics would need to develop an SOP for sponsors to meet with FDA officials about the status of their applications. An established procedure for meeting with the FDA will ease product sponsors and increase transparency about the regulatory process.

Sixth, an Office of Companion Diagnostics will need to develop a guidance discussing the necessity of cross-labeling products or providing mutually conforming labeling for products.

Finally, an Office of Companion Diagnostics will need to address post-marketing issues. Specifically, the Office of Companion Diagnostics will need to issue rules, again through

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[270] *See* FDA, *RFD Process*, http://www.fda.gov/CombinationProducts/RFDProcess/ (describing process by guidance is issued by other centers).

[271] 5 U.S.C. § 553 (2014).

[272] FDA, *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*, 33-35 (Oct. 2013), http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf.

[273] *Id.* at 33.

[274] *Id.* at 11 (discussing that the FDA is responsible for ensuring the safety and efficacy of medical devices).

notice and comment rulemaking, covering current Good Manufacturing Processes and Post Marketing Safety Regulations.

1. Reality of Regulatory Process

After reviewing the necessity of an Office of Companion Diagnostics and the steps required to create one, it's necessary to understand how this office would realistically operate. For instance, hypothetically, if Manufacturer X has developed drug Q and its companion diagnostic K, how would an Office of Companion Diagnostics help move Q and K through the regulatory process?

In this hypothetical, X would submit applications to the Office of Companion Diagnostics for Q and K. The Office of Companion Diagnostics would do an initial review of the applications and create two tentative timelines for the regulatory process for Q and K. One timeline would be created for the product sponsors so they have notice of how long the process will take. As product sponsors will be paying user fees, a suggested timeline should be about six months. The second timeline would be a more detailed internal agency document that would be sent to the various involved FDA Centers and would contain estimated deadlines for each stage of the regulatory process.

The Office of Companion Diagnostics would then assign the applications to specific experts within the Centers.[275] The Office would create a schedule of meetings for the experts from the Centers to meet with each other to discuss overlapping data and whether clearance will be contemporaneous. The first meeting between experts of different Centers will occur after these experts have had time to do an initial review of the applications.

For K, CDRH will apply a risk-based approach to determine the appropriate regulatory pathway, either a PMA or a 510(k). There are three risk classifications for medical devices (Class I, Class II, and Class III), which govern the level of FDA scrutiny necessary prior to marketing.[276] Device classifications depend on the claimed intended use and the indications of the device.[277] Class I devices are generally considered low risk, and are usually exempt from premarket clearance requirements such as submission of a 510(k) premarket notification.[278] Class II devices are considered to carry moderate risk and are reviewed for substantial equivalence to legally marketed products that have clearance for the same intended use by the premarket notification.[279] Class III devices are considered high-risk devices that are "life-saving" or "life-sustaining" and the majority of these devices require submission of a premarket approval application.[280] Companion diagnostics have been subject to Class III designations, and will likely continue to be.[281]

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275 *Guidance for Industry and FDA Staff: Application User Fees for Combination Products*, FDA, *supra* note 239 at 2(describing process by which OCP assigns applications).

276 Noviel et al., *The Rise Of Companion Diagnostics In Personalized Medicine*, *supra* note 264 at 2.

277 *Id.*

278 *Id.*

279 *Id.*

280 *Id.*

281 *Id.*

This is because they will be deemed as high-risk devices that will be used by health care professionals to determine if a patient should receive or discontinue a life-saving or life-sustaining drug.[282] Furthermore, most companion diagnostics will not have a predicate device to cite in a 510(k) submission.[283] Notably, companion diagnostics approved through the PMA process may be eligible for a patent term extension.[284]

For Q, CDER or CBER will review the two adequate and well-controlled clinical studies submitted with the application for safety and efficacy. CDER and CBER will also keep in mind whether the therapeutic product may be necessary to treat a serious or life-threatening condition where there is no satisfactory alternative treatment and the benefits outweigh the risk of not having the companion diagnostic.[285]

Once the Centers have done an initial review, they will meet to determine how likely it would be for the companion diagnostic and its corresponding therapeutic product to be cleared contemporaneously.[286] If the products will not be cleared contemporaneously, the Office of Companion Diagnostics will have an SOP for the product sponsors so the sponsors can address any marketing and business development concerns.[287] This SOP should include a written explanation sent to product sponsors about why the products will not be cleared contemporaneously, an estimate as to when each product will be cleared, and an opportunity for the product sponsors to meet with the Office of Companion Diagnostics to address any concerns.

After the experts from the Centers have met, they will continue with their normal individual review processes, and meet as necessary to address questions and concerns as they arise. Once the Centers have finished their reviews, they will meet one last time to finalize their decisions regarding approval and clearance, and then issue a written notification to the product sponsors.

The Office of Companion Diagnostics will have an SOP for the product sponsors to meet in person to address any concerns or possibly appeal the decision.

CONCLUSION

While this paper does not address every necessary step and action to make an Office of Companion Diagnostics a reality, it adds to the growing debate and conversation. Personalized medicine is growing and is the future for the practice of medicine.[288] While drugs, biologics, and devices have traditionally been independently regulated,

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[282] *Id.*

[283] *Id.*

[284] *Id.*

[285] FDA, *In Vitro Companion Diagnostic Devices*, *supra* note 189 at 9.

[286] *Id.* at 8.

[287] This hypothetical assumes that the product sponsor may be one sponsor that is developing both products. It is possible that two different sponsors can be sponsoring the therapeutic product and its companion diagnostic. In that scenario, for the purposes of a hypothetical situation, it is assumed that they have come to an agreement that aligns both of their interests.

[288] FDA, *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*, *supra* note 272 at 10.

they are becoming more and more intertwined.[289] As the field of companion diagnostics and corresponding therapeutic products grows, the FDA will need to adapt in order to maintain its regulatory authority. Furthermore, the creation of an Office of Companion Diagnostics will likely require a great deal of logistical planning, assistance from Congress, and a great deal of rule-making. However, it will be worth it because all stakeholders will benefit. Most importantly, patients will benefit, which is the ultimate goal. As President Obama said in his 2015 State of the Union, we can "lead a new era of medicine."[290]

[289] Combination Products Coalition, Op Ed*, supra* note 170.

[290] President Barack Obama, State of the Union (Jan. 20. 2015) (video and transcript available at https://www.whitehouse.gov/the-press-office/2015/01/20/remarks-president-state-union-address-january-20-2015).

How the Food and Drug Administration Could Use the Power of Publicity to Minimize Harm and Maximize Safety of Regulated Products

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INTRODUCTION

Throughout the course of its existence, the Food and Drug Administration (FDA) has been a somewhat overlooked entity. That is, until the FDA proclaims that something on the American market available to consumers or doctors is unsafe or dangerous. The FDA is responsible for regulating almost all foods consumed by humans, domestic animals, and livestock.[1] In addition, the FDA regulates drugs, medical devices, biologics, cosmetics, and radiation-emitting devices. In 2015, the FDA issued an average of 12.5 press releases each month.[2] In contrast, the U.S. Department of Health and Human Services, which has similar goals of American consumer health and protection, issues an average of 7.5 press releases each month.[3]

Press releases containing adverse publicity, e.g., that products or classes of products carry even the possibility of harm to the public, can be extremely harmful to the products' manufacturers occasionally compelling the manufacturers to voluntarily withdrawing the product.[4] Traditionally, the FDA has enforced its statutory mandate by halting production or seizing tainted items before they reach the consumer market.[5] However, the FDA may be increasing its impact by relying more on press releases that warn the public that products might carry some harm, whether it is proven or unproven.[6] And in today's world of breaking news stories getting through to the general public through social media platforms like Twitter (which limits each post to 140 characters or less), FDA press releases on the internet can create more misinformation and panic for consumers and manufactures alike with every re-tweet.[7]

In addition, the FDA may use negative press releases as a threat, to effectively pressure manufacturers to comply with regulations or voluntarily recall products. Manufacturers may decide to incur the costs of voluntary compliance, instead of seeing their brands harmed. In 1959, the FDA broadly announced that cranberries harvested in Washington State and Oregon might be hazardous, because they had been treated with pesticides that caused cancer in laboratory rats.[8] While the FDA warning may have had some

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[1] 21 U.S.C. §§ 332, 334, 375 (2014) (outlining the FDA's role); *but see* §§ 607(d) and 457(c) (delegating the U.S. Food Safety and Inspection Service (FSIS) to regulate the U.S. commercial supply of meat, poultry, and egg products).

[2] *Press Announcements*, FDA, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2015/default.htm.

[3] HHS, *2015 News Releases* (June 30, 2015), http://www.hhs.gov/news/press/2015pres/2015.html.

[4] Ernest Gellorn, *Adverse Publicity by Administrative Agencies*, 86 Harv. L. Rev. 1380 (1973) (arguing that the FDA has made inaccurate statements that have adversely affected the regulated entities).

[5] *Id.*

[6] *Id.*

[7] Michael Barthel et al., *The Evolving Role of News on Twitter and Facebook*, Pew Research Center (July 16, 2015), http://www.journalism.org/2015/07/14/the-evolving-role-of-news-on-twitter-and-facebook/ (explaining that social media users across demographics increasingly use social media platforms as their main source of news, especially news events as the events are happening which can lead to misinformation).

[8] Lisa M. Willis, Third-Year Paper, *No Cranberries for Thanksgiving: The Impact of FDA Adverse Publicity* (2005), Legal Electronic Document Archive, http://dash.harvard.edu/bitstream/handle/1/8889457/Willis05.html?sequence=2.

positive effect, it failed to mention that only 1 percent of the cranberries grown in that region were contaminated.[9] As a result, many perfectly good cranberries went unsold and producers were unduly harmed.[10] This example demonstrates the significant impact of one public statement from the FDA.[11]

In the hyper-connected modern age, an FDA press release can impact manufacturers and consumers in a matter of minutes. In recent years, the FDA, recognizing that press releases are influential and cost-effective, has used them more and more often to regulate products, particularly medical devices.[12] Overall, the numbers of FDA injunctions and seizures have increased proportionally with the amount of recall events within the press releases. However, these numbers are steadily increasing each year.[13] Unfortunately, thus far, the FDA's press releases have not been wholly accurate.[14] Quite often, the press releases contain *alleged* violations, which the internet can inflate, misreport, and spread incredibly fast. The FDA has failed to use their power of publicity in a way that best guides consumers and manufacturers alike. In order to better this unfortunate use of power, the FDA must recognize that when adverse publicity is made available to the public, the effects of such publicity go beyond the product or good at issue. Once that is recognized, the solution is another obstacle the agency must face in the modern internet age of irrevocable statements. Through an in-depth look at the handling of one medical device, the issues of the FDA's use of publicity will be assessed, possible solutions to the overall problem observed. Such solutions will then be addressed, hypothetically, to the problem at issue in order to demonstrate how the FDA could potentially reign in its abuse of publicity in such a fashion that would benefit all parties.

I. THE PROBLEM

Publicity has many benefits because it can quickly alert consumers of hazardous products. However, adverse publicity can cause undue harm on the manufacturers, that may outweigh the benefit to consumers. Adverse publicity may be viewed as the deprivation of a private person or firm's right to engage in commerce and free enterprise, without the due process of law normally associated with government action.[15] In other words, if the government makes a negative statement about a private actor or its product, the private actor has no recourse, even if the statement is false.[16] The private actor can only

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[9] *Id.* at 6.

[10] *Id.*

[11] 21 U.S.C. § 375 (2014).

[12] *FDA Enforcement Statistics Summary Fiscal Year 2012*, FDA (2013), http://www.fda.gov/downloads/ICECI/EnforcementActions/UCM346964.%20pdf.

[13] *Id.*

[14] *See infra* notes 20-23 and accompanying text (arguing that the FDA wrongly banned importation of *all* fruits grown in Chile, after receiving warning that grapes grown in Chile had been poisoned and finding two punctured grapes in the U.S. market).

[15] Shannon E. Johnson, Third-Year Paper, *Publicity and the FDA, An Update* (1997), Digital Access to Scholarship at Harvard, http://dash. harvard.edu/bitstream/handle/1/8846783/sjohnson.pdf?sequence=1.

[16] *Id.*

hope the government uses common sense and does not abuse its discretion.[17] Moreover, judicial review and potential monetary compensation for market losses cannot undo the widespread effects of erroneous adverse publicity because, with sovereign immunity, such judicial review is unavailable to those injured.[18] A negative FDA press release can have lasting harm to a particular product's marketing or to a manufacturer's overall reputation, even if the press release is later proved to be true only in part.[19] For example, in the mid-1990s, the U.S. Embassy in Chile received two anonymous tips that grapes grown in Chile and shipped to the United States had been contaminated with cyanide.[20] The FDA then found puncture marks in two Chilean grapes, quickly concluded the anonymous tips must be true, and banned *all* Chilean fruits from entering the United States.[21] The FDA took this broad action even though it found no signs of contamination whatsoever in a second batch of Chilean grapes.[22] Unsurprisingly, Chilean fruit suffered economically in the American marketplace as a result of the scare generated from the FDA's press release regarding possible contamination.[23]

FDA press releases that mislead American consumers and the general marketplace have dramatic and widespread effects. Unfortunately, broad, initial negative statements about products attract more attention than subsequent corrections or retractions. In one study, 160 newspapers reported negative information about a product — but only half of those newspapers published a retraction.[24] Even when a statement is not an outright press release from the FDA, statements from sources viewed by the general public as associated with the FDA can still have negative consequences for those whom are concerned with the subject material.[25] Even though the FDA does not intentionally create this misunderstanding, it still causes great harm to the manufacturers and producers at issue.[26] For example, in summer 2014, FDA branch chief Monica Metz claimed, in the form of a constituent update posted on FDA's website, that the agency planned to ban the traditional technique of aging artisan cheeses on wooden shelves, citing the risk of bacteria growth.[27] It was not an official press release but still scared many American cheesemakers and cheese lovers.

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17 *Id.*

18 Federal Tort Claims Act (FTCA), 28 U.S.C. § 2680 (2014) (granting sovereign immunity to the government regarding "any claim based upon an act or omission of an employee of the Government, exercising due care, in the execution of a statute or regulation–or based upon the exercise or performance–on the part of a federal agency or an employee of the Government, whether or not the discretion involved be abused.").

19 Willis *supra* note 8, at 5 (writing that a press release can lead to product liability suits, brand rejection, and decreased stock market value).

20 *Fisher Bros. Sales, Inc. v. U.S.*, 46 F.3d 279, 282 (3rd Cir. 1995).

21 *Id.* at 287.

22 *Id.*

23 *Id.*

24 James T. O'Reilly, *Federal Information Disclosure,* § 25.01 (2015).

25 *Clarification on Using Wood Shelving in Artisanal Cheesemaking*, FDA (June 11, 2014) http://www.fda.gov/Food/NewsEvents/ConstituentUpdates/ucm400808.htm.

26 *Id.*

27 *Id*.

Considering the FDA's influence, it must exercise greater caution before issuing negative information about consumer products. If the FDA reasonably believes, but has not confirmed, that a product will threaten American consumers' lives, it may need to disseminate a warning immediately. In a situation like this, an immediate and effective press release can be a great exception to the need for caution and careful steps. Unfortunately, the FDA has not created any procedure for this kind of exceptional situation, which would probably require consultation with outside experts and an immediate recall of the product.[28] The FDA would benefit from such a procedure: for example, it would have been extremely helpful in early 2014, when the FDA first encountered a crisis centering on power morcellators.[29] This crisis has continued for months and has even prompted the U.S. House of Representatives to call for an investigation of the FDA's regulation of medical devices.[30]

Another growing concern is that the FDA fails to perform the investigations and audits that may help regulated entities to comply voluntarily and avoid adverse publicity.[31] In 2011, the FDA failed to perform its own audits of facilities associated with food preparation in one-third of U.S. states; instead, it relied on state entities' inspections of those facilities.[32] The FDA has also reduced its staff and conducted fewer food product safety tests, even as manufacturers have initiated a greater number of food recalls, over the past fifteen years.[33] Instead, the FDA has used broadly worded and inexpensive press releases to compel manufacturers to voluntarily recall their products.[34] If the FDA continues to use press releases to enforce its regulations, it must try to decrease the chance of undue alarm and misinformation, and not harm companies that are in full compliance with the FDCA.

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[28] *Power Morcellator Activist Protests FDA Failure to Ban Uterine Morcellation*, Bernstein Liebhard LLP (Nov. 11, 2014), http://www.prnewswire.com/news-releases/power-morcellator-activist-protests-fda-failure-to-ban-uterine-morcellation-bernstein-liebhard-llp-reports-281323621.html (discussing Dr. Amy Reed, doctor and cancer patient who underwent surgery with the device at issue, campaigning for the outright recall of the laparoscopic power morcellator, a medical device used in minimally invasive surgeries, and furiously upset with the lack of action and several months of time the FDA spent considering an outright recall of the medical device that possibly causes uterine cancer).

[29] *Id.*

[30] Jennifer Levitz, *House Passes Bill to Improve Safety Monitoring of Medical Devices*, Wall St. J. (July 12, 2015) *available at* http://www.wsj.com/articles/house-passes-bill-to-improve-safety-monitoring-of-medical-devices-1436736213.

[31] *Vulnerabilities in FDA's Oversight of State Food Facility Inspections*, HHS Office of Inspector General (2011), http://oig. hhs.gov/oei/reports/oei-02-09-00430.pdf.

[32] *Id.*

[33] David Morgan, *Despite Food Scares, FDA Cuts Inspections*, CBS (Feb. 26, 2007), http://www.cbsnews.com/news/despite-food-scares-fda-cuts-inspections/.

[34] FDA Enforcement Statistics Summary Fiscal Year 2013, *supra* note 12.

II. UNDERSTANDING THE OBSTACLE

A manufacturer unduly harmed by an inaccurate or overblown press release has little recourse, largely because the FDA has broad discretion to act against *potentially* harmful products.[35] Furthermore, the Federal Tort Claims Act (FTCA) generally protects federal government entities from liability.[36] As a result, the FDA can only be found liable for breaching its duty of care.[37] However, since Congress has declared that the FDA alone has the expertise to ensure that foods, drugs, and medical devices are safe for public use, courts are unlikely to second-guess the FDA's decisions.[38] This discretion is reflected in the Administrative Procedures Act ("APA"), which directs courts to defer to most decisions by the FDA and other administrative agencies.[39] Consequently, it is quite unlikely that a court will find that the FDA erred when the agency issued a precautionary press release.[40] Upon creating the FDA, Congress primarily intended to do away with Sinclairian producers and manufacturers.[41] Congress simply assumed that the FDA would exercise good reasoning while seeking to improve health and safety in the American marketplace.

When adverse publicity results in a company's demise, it is difficult to build each necessary part of the case against the FDA. First, a plaintiff must exhaust all available agency remedies and fulfill other difficult requirements to overcome the FTCA's general grant of sovereign immunity.[42] Even then, the plaintiff must demonstrate that the FDA's negative press release caused its economic harm.[43] It will be difficult to establish that the FDA's statements about a company's alleged violations of the FDCA proximately caused consumers to abandon the company's products. It is possible that consumers simply preferred competing products and the market worked as it should. Even if the plaintiff can prove causation, the plaintiff must then prove its harms. These hurdles may dissuade some plaintiffs for even seeking judicial redress.

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[35] 28 U.S.C. § 2680 (2012) (granting discretion to the FDA and limiting judicial review of the FDA's actions).

[36] *Id.*

[37] Mark Niles, *Nothing but Mischief: The Federal Tort Claims Act and the Scope of Discretionary Immunity*, 54 Admin. L. Rev. 1275 (2002).

[38] 21 U.S.C. § 393(b)(2)(A) (2012).

[39] Administrative Procedure Act, 5 U.S.C. § 706 (2012) (providing that judicial review is only warranted when administrative agencies act contrary to, or in excess of, statutory or constitutional authority).

[40] *See* Lars Noah, *Governance by the Backdoor: Administrative Law(Lessness?) at the FDA*, 93 Neb. L. Rev. 89, 128 (2014) (suggesting that adverse publicity is a form of a procedural short cut that the FDA uses to avoid judicial proceedings).

[41] *See generally* Upton Sinclair, The Jungle (See Sharp Press 2003) (1906) (exposing hazardous conditions and health code violations of workplaces within the meat-packing industry).

[42] *See* 5 U.S.C. § 704 (outlining administrative exhaustion requirement).

[43] *Mizokami v. United States*, 414 F.2d 1375, 1376-77, 1381 (Ct. Cl. 1969) (obtaining a private bill from Congress to waive FDA's sovereign immunity and determining that "sufficient connection had been proven between the [FDA]'s actions and the alleged losses"). In *Mizokami*, a private law allowed plaintiff vegetable growers who claimed that their spinach crops were contaminated with pesticides to file suit against FDA. *Id.* at 1376-77. Along with waiving FDA's immunity, the bill also outright conceded to FDA's liability for the actions and left it to the court to decide damages for growers. *Id.* at 1379.

A negative press release has lasting effects on manufacturers and consumers. Adverse publicity lingers even after the information is found to be untrue.[44] Unfortunately, the FDA rarely issues corrections and retractions; when the FDA does, it receives much less attention, and it might create even more confusion about whether the products are safe.[45] Specifically, the FDA only revisits a negative statement after determining that everything possible to improve or completely remove the product from the market has been done, and after several FDA offices coordinate in writing with one another.[46] Therefore, it is difficult for manufacturers to recover from adverse publicity.

A. Internet Pains and Not Enough Gains

The FDA's failings in issuing press releases, which potentially cause undue recalls and consumer misinformation, are compounded by the nature of the World Wide Web. Most unfortunately, the "Internet serves as a content multiplier, and when capital markets seize information without verifying the details, the velocity and severity of the fallout can be even greater."[47] The FDA and other government agencies particularly struggle to communicate accurately over social media sites like Twitter, which call for a brief statement and a link to a formal press release. The FDA's recent social media campaign through the FDA Adverse Event Reporting System (FAERS) is a perfect example.[48] This proposed system would search the Internet for adverse events involving regulated products, which have not yet been reported to the FDA.[49] The FDA's guidance document on the proposed system focuses on how food and drug manufacturers should be properly labeling and marketing their products on social media outlets.[50] It even discusses how to address Twitter's 140-character limit.[51] The system would empower consumers to report perceived violations of the FDCA directly

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[44] *See* Nathan Cortez, *Adverse Publicity by Administrative Agencies in the Internet Era*, 2011 BYU L. Rev. 1371, 1403 (2011) (suggesting that the FDA often acts on "limited information and scientific uncertainty").

[45] *See* 21 C.F.R. § 7.55(a) (2015) (outlining the steps for terminating an FDA recall).

[46] *Id.* A recall will be terminated when the Food and Drug Administration determines that all reasonable efforts have been made to remove or correct the product in accordance with the recall strategy, and when it is reasonable to assume that the product subject to the recall has been removed and proper disposition or correction has been made commensurate with the degree of hazard of the recalled product. Written notification that a recall is terminated will be issued by the appropriate Food and Drug Administration district office to the recalling firm.

[47] Cortez, supra note 44 at 1401.

[48] *Mining Social Media for Adverse Event Surveillance*, FDA, http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm455305.htm.

[49] *Id.*

[50] Thomas Abrams, *FDA Issues Draft Guidances for Industry on Social Media and Internet Communications About Medical Products: Designed with Patients in Mind,* FDA Voice Blog (June 17, 2014), http://blogs.fda.gov/fdavoice/index.php/2014/06/fda-issues-draft-guidances-for-industry-on-social-media-and-internet-communications-about-medical-products-designed-with-patients-in-mind/.

[51] *Guidance for Industry Internet/Social Media Platforms with Character Space Limitations— Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices (Draft Guidance)*, FDA (2014), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401087.pdf

to the FDA.[52] However, many commentators, including physicians, were quite dubious that the FDA would be able to process and analyze these reports.[53] It could simply be seen as the FDA trying to keep up with the times.

In general, consumer panic about a particular product could prevent the manufacturer from telling its side of the story and might lead to the collapse of that manufacturer or the entire industry. As long as the internet remains an unfiltered and unregulated world of bloggers and news watchdogs, the FDA must attempt to issue accurate statements and discourage the public from overreacting and furthering unfounded allegations.[54]

The FDA's use of the internet has only intensified its ability to create adverse publicity. There is a grave possibility that FDA statements will spread too quickly and become distorted before manufacturers can properly respond.[55] Furthermore, the FDA is not required to give advanced notice to manufacturers before issuing press releases.[56] Manufacturers may be caught entirely off-guard and may struggle to respond accurately and effectively to the public and to government regulators.

The FDA's broad communication can reach consumers in numerous ways. In print alone, agency publications like the FDA Consumer reach a circulation of more than 25,000 paid subscribers.[57] Furthermore, an individual may sign up for multiple FDA mailing lists, which can add up to 4 emails a day. This high number of original communications from the FDA can then become twisted and misconstrued on the internet as they are removed and become indirect communications, in ways that even the most sensationalist newspapers of the FDA's early days could not imagine because of the multiple levels between the actual source and what the audiences consumes.[58] So when an initial press release is inaccurate or incomplete, it is even more likely that the press release's dissemination on the internet will create panic.

While the FDA cannot control everything that is said on the Internet or in the press, the FDA should maintain better control, self-restraint, and due diligence in making sure that its press releases are as factually sound and clear as possible.[59] Such control could include consulting with experts outside of the agency when necessary and investigating matters further before releasing negative press releases, especially when there are no members of the FDA specialized and duly prepared to assess a particular product.

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[52] *See* Abrams, *supra* note 50 (emphasizing that the focus of the social media project is safety for the consumer).

[53] Lena J. Weiner, *FDA's Social Media Gambit 'A Long Shot,' Says Patient Advocate*, Health Leaders Media (August 13, 2014 6:45 AM) http://www.healthleadersmedia.com/page-1/QUA-307343/FDAs-Social-Media-Gambit-A-Long-Shot-Says-Patient-Advocate##.

[54] *See* Cortez, *supra* note 44, at 1395 (discussing the likelihood of data being misinterpreted through social media).

[55] *Id*.

[56] Johnson, *supra* note 15, at 10.

[57] *Id.* at 13.

[58] Cortez, *supra* note 44, at 1371.

[59] *Id.* at 1376.

B. What the FDA World Needs Now

Consumers, manufacturers, and retailers alike deserve a better process through which they can learn about truly dangerous or unsafe products. The FDA should only communicate reliable, factual, and timely information about investigations of products and manufacturers, including whether those investigations are pending or completed. In addition, the FDA must consider the public's likely reaction before making any announcement, to minimize the possibility of harm and maximize the potential of protecting consumers. In other words, the FDA should inform consumers about dangerous products, but should not push consumers to become hostile towards any brand or industry. By striking this balance, the FDA can ensure consumer safety without creating undue consumer panic.

III. THE PROBLEM AS FOUND IN TODAY'S HEADLINES

A. The Tragedy

The FDA demonstrated its ability to create chaos and confusion in its recent treatment of the laparoscopic power morcellator (LPM). An LPM is used to perform hysterectomies (surgical removal of the uterus) and myomectomy (surgical removal of uterine fibroids).[60] FDA regulation of the LPM began, like its regulation of many products, with tragedy. Specifically, the FDA took notice of Dr. Amy Reed's campaign to demonstrate how a common procedure used to remove otherwise benign uterine fibroids from women could actually lead to cancer.[61] Fibroids are common, benign uterine growths that can be easily removed and most of the time are recommended to be removed, as the growths could later become cancerous.[62] However, the LPM was found, in certain cases, to leave behind portions of the fibroid within the woman's uterus and become malignant some months, or sometimes sooner, after the procedure.[63] After this occurred to Dr. Reed, she resolved to publicize the procedure's risks.

The LPM's use in myomectomies has been and continues to be praised by some.[64] In April 2014, the FDA estimated that this surgery is performed at least 50,000 times in the United States each year.[65] It is minimally invasive, requires very little recovery time, and generally succeeds at removing uterine fibroids from a place where they would be too small to develop samples to test for cancer prior to the fibroids removal.[66] The LPM's spinning blade slices fibroid tissue into smaller pieces and removes those pieces

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[60] *FDA Discourages Use of Laparoscopic Power Morcellation for Removal of Uterus or Uterine Fibroids*, FDA (April 17, 2014), http://www.fda.gov/*NewsEvents*/Newsroom/PressAnnouncements/ucm393689.htm (hereinafter FDA, *April 2014 Press Release*).

[61] Jennifer Levitz & Jon Kamp, Deadly Medicine: A Common Surgery for Women and the Cancer It Leaves Behind 34, 53, 67 (Wall St. J. ed. 2014).

[62] *Id.* at 9-12.

[63] FDA, *April 2014 Press Release*, *supra* note 60.

[64] Levitz & Kamp, *supra* note 61, at 49-50, 56.

[65] *Id.* at 23.

[66] *Id.* at 9-10, 12-13.

through small incisions.[67] This procedure may be performed with a bag to catch spare pieces of the fibroids that can spread into the uterus.[68] Unless the gynecologist uses a bag with the LPM, some of the fibroid fragments may spread and be left behind in the uterus after surgery. [69] However, gynecologists routinely used the LPM device without a bag in removing uterine fibroids.[70]

Dr. Reed, an anesthesiologist and mother of six, is attempting to use her own experience to push the FDA to regulate the LPM. She had the basic surgery to remove uterine fibroid tumors using the LPM, but eight days later, she learned it had worsened her prognosis by spreading cancer from the remaining uterine fibroids.[71] The shredding of the fibroid inadvertently spread the undetected cancer because the fragments were uncontained.[72] Throughout fall 2014, while Dr. Reed's cancer had progressed to stage four, her husband focused on writing letters to the FDA, questioning its failure to act about the potentially deadly medical device.[73] While many agree with Dr. Reed's calls for action, others argue that the device is safe and that the FDA created a mountain out of a few exaggerated facts.[74]

At the time of this writing, Dr. Reed had a recurrence of her cancer, a tumor in her spine, but that has not stopped her avid fight for justice.[75] She is now involved in an FBI investigation about whether the device's manufacturer, Johnson & Johnson, knew about the risks as early as 2006.[76] Dr. Reed argues that she and other patients should have been better protected and this story involves "a violation of federal law that has led to the loss of life."[77]

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[67] Jon Kamp, *More Health Insurers Take Action to Curb Morcellator Use,* Wall St. J. (Apr. 2, 2015), *available at* http://www.wsj.com/articles/more-health-insurers-take-action-to-limit-morcellator-use-1428009386.

[68] *Id.*

[69] Levitz & Kamp, *supra* note 61, at 24.

[70] *Id*. at 24-25.

[71] *Id.* at 13-15.

[72] *Doctor with Cancer Raises Alarm about Medical Device*, CBS News (June 4, 2015), http://www.cbsnews.com/news/doctor-with-cancer-morcellator-medical-device/.

[73] Bernstein Liebhard LLP, *supra* note 28.

[74] Jennifer Levitz & Jon Kamp, *Gynecologists Resist FDA Over Popular Surgical Tool,* Wall St. J. (Sept. 21, 2014), *available at* http://www.wsj.com/articles/gynecologists-push-back-on-fdas-caution-about-cancer-when-using-morcellation-in-hysterectomies-1411358341 (reporting that obstetrics and gynecologists alike were split over the use LPMS in myomectomies, even after the FDA discouraged their use); *see also* Jon Kamp, *J&J's Exit from Morcellator Sales Leaves Opportunities for Others*, Wall St. J. (Sept. 23, 2014), http://blogs.wsj.com/corporate-intelligence/2014/09/23/jjs-exit-from-morcellator-sales-leaves-opportunities-for-others/.

[75] CBS News, *supra* note 72.

[76] *Id.*

[77] *Id.*; *see also* Bernstein Liebhard LLP, *supra* note 28.

B. The First Press Release

In April 2014, the FDA issued its first press release regarding the LPM.[78] However, the press release simply asked doctors to *reconsider* the possibilities of harm posed by use of the LPM: a less than useful recommendation. With separate statements of caution, warning, and urging of doubt regarding the procedure's benefits and risks, the FDA's press release revealed that the benefits of the device may be limited due to the potential development after surgery, of uterine sarcoma, that had not been found or realized prior to surgery.[79] The release itself was extremely limited and offered little research data or clarity about the device's use in the future.[80] However, the press release did claim that the LPM causes cancer in 1 in 350 women and further stated:

> There is a risk that the procedure will spread the cancerous tissue within the abdomen and pelvis, significantly worsening the patient's likelihood of long-term survival. For this reason, and because there is no reliable method for predicting whether a woman with fibroids may have a uterine sarcoma, the FDA discourages the use of laparoscopic power morcellation during hysterectomy or myomectomy for uterine fibroids.[81]

The FDA admitted that this reasoning was based on only a survey of the small amount of information on the dangers of the medical device available at the time.[82] While the concern for the medical device had been slowly growing since approximately 2006, available information and studies about the device had unfortunately not increased. In the April 2014 press release, the FDA also promised that an advisory committee would review the device's risks in more detail that July.[83] Unfortunately, that committee only conducted a general review of nine studies (one of which was only in abstract form).[84]

For the next five months, the FDA did not take any further actions regarding this potentially cancer-inducing surgical device. During the FDA's period of silence, individual and institutional providers offered their opinions about whether the device should remain on the market.[85] Many also criticized the FDA for discouraging use of the device but not actually recalling the device or offering any conclusive answers.[86]

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[78] FDA, *April 2014 Press Release*, *supra* note 60.

[79] *Id.*

[80] *Id.*

[81] *Id.*

[82] Levitz & Kamp, *supra* note 61, at 56.

[83] Jennifer Levitz, *FBI Eyes Hysterectomy Device Found to Spread Uterine Cancer,* Wall St. J. (May 28, 2015), *available at* http://www.wsj.com/articles/fbi-is-investigating-surgical-device-1432746641; *Quantitative Assessment of the Prevalence of Unsuspected Uterine Sarcoma in Women Undergoing Treatment of Uterine Fibroids: Summary and Key Findings* (2014), FDA, *available at* http://www.fda.gov/downloads/MedicalDevices/Safety/AlertsandNotices/UCM393589.pdf (explaining limited studies conducted over the past 30 years) (hereinafter FDA, *Quantitative Assessment*); FDA, *April 2014 Press Release*, *supra* note 60.

[84] FDA, *Quantitative Assessment*, *supra* note 83.

[85] Levitz & Kamp, *supra* note 61, at 55, 77.

[86] *Id.* at 55.

C. The Reaction

Following the FDA advisory committee's July 2014 meeting on the LPM numerous U.S. doctors and hospitals, citing years of mistrust of the LPM, asked the FDA to announce a complete recall.[87] The leading LPM manufacturer, Johnson & Johnson, announced that it would keep its version from the market until the FDA made a conclusion about the LPM's safety.[88] BlueCross/BlueShield, Highmark, and other health insurance providers quickly followed suit by discontinuing reimbursement for procedures that used the LPM.[89]

However, this was not a one-sided debate. Other patients, doctors, hospitals, and manufacturers argued that the FDA was making a mountain out of a perfectly fine and functional molehill.[90] Many wondered whether the FDA had overstepped its boundaries by declaring that 1 in 350 women treated with the LPM would develop cancer, without offering conclusive support for that statement.[91] Some doctors proposed that the FDA's risk analysis was incorrect and that the actual risk of undetected sarcoma developing after the surgery was more likely to be 1 in 300.[92] Some commentators suggested that the FDA should have considered patients' ages, history of other cancers, and other traits that might have affect the benefits and risks of using the LPM to remove fibroids.[93] While manufacturers and healthcare providers had varying opinions about the LPM, it became clear that those opinions could have helped FDA earlier in the process.

D. The Second Press Release

On November 24, 2014, the FDA issued a second press release that further discouraged use of the LPM to remove uterine fibroids.[94] The FDA then suggested that "immediately in effect," LPM packaging should include two additional safety warnings.[95] First, the packaging should display a "black box warning"[96] disclosing that the operation could increase the risk of spreading cancer throughout the body and worsen the patient's likelihood of long-term survival.[97] Second, the packaging must list contraindications for

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87 *See id.* at 55-56; Bernstein Liebhard LLP, *supra* note 28.

88 Levitz & Kamp, *supra* note 61, at 54.

89 Roopal Luhanna, *Blue Cross/Blue Shield Ends Coverage for Power Morcellation in 3 States*, Legal Examiner (Sept. 12, 2014), http://newyork.legalexaminer.com/defective-dangerous-products/blue-crossblue-shield-ends-coverage-for-power-morcellation-in-3-states/; Kamp, *supra* note 67.

90 Levitz & Kamp, *supra* note 74.

91 *Id.*; *see also* Levitz & Kamp, *supra* note 61.

92 Levitz & Kamp, *supra* note 61.

93 *Id.* at 54, 63-64; FDA, *Quantitative Assessment*, *supra* note 83.

94 *FDA Warns Against Using Laparoscopic Power Morcellators to Treat Uterine Fibroids*, FDA (Nov. 24, 2014), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm424435.htm (hereinafter FDA, *Nov. 2014 Press Release*).

95 *Id.*

96 21 C.F.R. § 201.57 (2015) (providing that a black box warning is the strongest warning manufacturers may be required to display on their products).

97 FDA, *Nov. 2014 Press Release*, *supra* note 94.

use of the LPM.[98] Overall, the second FDA press release encouraged doctors to have more discussion of the LPM's risks and benefits with their patients.[99] The FDA further promised that it would continue monitoring adverse event reports and information as it became available on the medical device to protect public health.[100] However, the FDA's assurance could be viewed as insufficient given the delayed warning.

E. The Silver Lining

Before the FDA's advisory committee convened and issued its conclusions in its second press release, other stakeholders — manufacturers, doctors, hospitals, and insurers– conducted their own fruitful discussion. However, one group above all clearly benefited from the FDA's final conclusion: women considering procedures using the LPM. Following the FDA's second press release, those women and their providers better knew what to consider before choosing to use the LPM. The FDA was most useful when it organized and disclosed all of the stakeholders' competing arguments and helped patients to make their own informed decisions.

The FDA's actions prompted each patient and her doctor to engage in a more sustained dialogue about whether to use the LPM. The FDA has also prompted doctors to ask patients to sign informed consent forms before undergoing procedures, to share videos of the LPM's use with other doctors, and to keep asking whether the LPM surgery is the best option for each patient.[101] So while the FDA took almost five months to issue its much-needed second press release, the FDA did help to initiate conversations between patients and doctors. Admittedly, during the delay, patients and other stakeholders may have begun to rely on the FDA's inaction and may have concluded on their own that the FDA would not issue a recall of LPMs. However, either way, the process was beneficial because patients began reviewing their options and making more educated decisions.

Despite this eventual success, the FDA has been criticized for its handling of the LPM device. For example, a majority of doctors surveyed by the Wall Street Journal agreed that the FDA should update its methods of regulating medical devices such as the LPM.[102] Other government agencies are reviewing the FDA's actions and trying to ensure that this does not happen again. The FBI is currently considering the FDA's ability to effectively regulate medical devices, specifically since it initially approved the LPM, which clearly carries some risks.[103] The FBI is conducting a second, separate investigation centering on the LPM itself.[104] While the FBI acknowledges that the FDA made the right moves toward resolving the issue with the medical device by requiring

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[98] *Id.*; *Contraindication,* Merriam-Webster Dictionary, http://www.merriam-webster.com/dictionary/contraindication (defining contraindication as "something (as a symptom or condition) that makes a particular treatment or procedure inadvisable.").

[99] FDA, *Nov. 2014 Press Release*, *supra* note 94.

[100] *Id.*

[101] Levitz & Kamp, *supra* note 61, at 12.

[102] Thomas M. Burton, *Do the FDA's Regulations Governing Medical Devices Need to Be Overhauled?*, Wall St. J. (Mar. 23, 2015), http://www.wsj.com/articles/do-the-fdas-regulations-of-medical-devices-need-to-be-overhauled-1427079649.

[103] Levitz, *supra* note 83.

[104] *Id.*

new warning labels on the product, the FBI is still seeking to find what information should have come to light before even the first FDA press release back in July 2014.[105] Finally, members of the U.S. House of Representatives, in response to the LPM crisis, have proposed an amendment to the "21st Century Cures" Act that would require more Congressional oversight on the FDA's methodologies in determining whether a device is "generally recognized as safe" for use in the marketplace.[106]

IV. RECOMMENDED SOLUTIONS

With some reforms, the FDA can better inform American consumers about medical devices and other consumer products. The FDA should ensure that the information in each press release is thorough and well-supported by sufficient facts.[107] The FDA should offer a notice and comment period to experts and stakeholders or should resolve all material questions before issuing a press release, whenever it is possible to do so.[108] The FDA should also consider the public's knowledge of a product and the potential for confusion, before rushing to issue a press release.[109] The FDA must also become more effective at retracting and correcting negative statements, to effectively inform the public and minimize undue harm to manufacturers.[110] In addition to FDA reforms, private actors harmed by adverse publicity should be able to seek compensation when they are harmed by inappropriate FDA action.[111]

The LPM crisis demonstrates that the FDA should also find some way to address emergency situations involving products that are already on the market. The FDA should establish a taskforce that will respond to tips received through the new FAERS system.[112] Finally, the FDA must amend and retract flawed statements more effectively.[113] This solution to the abuse and misuse of the FDA's power of publicity could come in the form of an adjustment to the Administrative Procedure Act (APA) or the FDCA itself, through the possible creation of an amendment to the FDCA. No matter where this amendment occurs, it should include a higher standard of proof and research behind each press release, notice to companies and industries prior to release, proper termination of recalls and the mandate of corrective press releases, increased overall self-restraint by the FDA,

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105 *Id.*

106 Levitz *supra* note 30.

107 Richard S. Morey, *FDA Publicity Against Consumer Products—Time for Statutory Revitalization?* 30 Bus. Law. 165-67 (1975) (explaining because of the large number of products regulated by FDA, manufacturers are particularly vulnerable to the adverse effects of recalls or the threat of recalls whether or not the recall is appropriate or the manufacturer feels it justified).

108 *See* Gellhorn, *supra* note 4, at 1431.

109 *Id.* at 1425-27, 1429 (comparing the reliability of an overflow of information on which agencies rely and exploring the effects of press releases across different agencies which can reduce agency credibility and benumb the public).

110 *See* Johnson, *supra* note 15.

111 *See* Cortez, *supra* note 44, at 1406, 1408 (recommending less dependency by the FDA on the protections of the APA and opening themselves up to more judicial review when there is actual harm).

112 *See* FDA, *Mining Social Media for Adverse Event Surveillance*, *supra* note 48

113 *See* Gellhorn, *supra* note 4.

and the creation of a task force that can quickly respond when there is a legitimate threat of seriously harmful products.[114]

A. Better Research

If the FDA is required to be more thorough and careful when drafting a press release, it will be less likely to cause harm.[115] Instead, the resulting press release will be more reliable and beneficial to the public.[116] Also, by always making sure that there is some level of outside, specialized expert opinion involved in a press release regarding the specific product and its functions, adverse publicity will be less likely to have misleading or incorrect information in it.[117] By mandating a minimum amount of time and research on a product prior to the press release, this amendment could occur without too much extra cost and time to the FDA. This higher standard could also decrease the amount of allegations that the FDA included in their press releases and further dispel the opportunity for misinformation as the information trickled through social media. The FDA could ban allegations in press releases altogether. Alternatively, in cases of more significant risk or substantial harm, when the FDA needs to issue press releases, it should require expert opinions and caveat the release by indicating the case is currently an allegation, or that it lacks complete information.[118]

B. Due Notice

Furthermore, the FDA should be required to offer some warning to manufacturers before suggesting publicly that the manufacturers have not complied with the FDCA. Due notice could mean that the FDA was required to give a reasonable amount of time for manufacturers and producers to be able to comment or even correct the issue that FDA found with the product, much like the standard voluntary recalls of the FDA.[119] Such a notice and comment period would protect manufacturers from undue adverse publicity.[120] It might allow manufacturers to voluntarily recall potentially harmful products while maintaining public goodwill. Reasonable notice could even be limited to when the pending press release contains significant risk to either public health or (and possibly one leading to the other) significant economic risk to the manufacturer upon disclosure of the press release.[121] More than likely, if the FDA were more susceptible to tort liability, the agency might be more willing to provide reasonable notice.

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114 *See* Cortez, *supra* note 44, at 1409 (arguing for a higher standard of proof); Gellhorn, *supra* note 4 (arguing for greater self-restraint by the FDA); Johnson, *supra* note 15; Willis, *supra* note 8, at 2 (arguing for faster and more attention-grabbing corrective press releases).

115 *See* Gellhorn, *supra* note 4.

116 *Id.*

117 *See* Johnson, *supra* note 15.

118 *Id.*

119 21 C.F.R. § 810 (2012) (granting the FDA the alternative method of regulation by recalling products when there is a defect in the produce by itself or in the labeling of the product).

120 Gellhorn, *supra* note 4, at 1431.

121 Johnson, *supra* note 15.

C. Proper Terminations & Corrective Statements

The FDA could also further the public health by becoming more willing and effective at amending or correcting press releases. The FDA should pay attention to new information and public response to its press releases, and respond when necessary. These back-end fixes to adverse publicity would provide some aid to manufacturers injured by misleading or misinformed press releases.[122] Corrective press releases would also considerably aid confused American consumers. Such follow-up press releases could report the final outcome of FDA investigations and summarize the underlying research and evidence.[123]

Given that the internet is a large cause of confusion and misinterpretation, the FDA could arguably try to oversee all internet commentary on FDA regulatory action.[124] Because the use of social media has become so prolific, the FDA should incorporate social media into FAERS to monitor the public's reaction to press releases and to seek out adverse events to address.[125] Through the FDA's acceptance of an additional medium to communicate with the public, it could effectively decrease the amount of misinterpretation of FDA press releases, especially those leading to adverse publicity. Integrating social media with FAERS will allow the FDA to promptly offer a corrective follow up press release to cease confusion through its FAERS operator.[126] Twitter's one hundred and forty characters will be feared no more.

D. Self-Restraint and Addressing Emergency Situations

Considering that the FDA's ability to create adverse publicity for manufacturers greatly predated the Internet, the FDA should exercise more self-restraint overall.[127] The FDA is responsible for regulating a great number of products, many of which are potentially harmful or misleading to the public. However, the FDA does not need to issue public press releases about each one of those violations unless they are emergency situations. By exercising some self-restraint, the FDA would demonstrate that it is truly dedicated to public health and would also improve its relationships with manufacturers.[128] Self-restraint by the FDA could also generate public support for a task force that will respond quickly to those products already on the market that pose imminent, serious threats to public health, but only when such a task force is completely necessary. With dedicated time and effort to study whatever available research exists and offer a recall or other advisement on the product as soon as trouble is found, such a task force would effectively guide the FDA to fulfilling its public service duty.

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122 *See generally* Willis, *supra* note 8 (giving the example of the 1956 "cranberry crisis").

123 *See* Gellhorn, *supra* note 4.

124 *See generally* Barthel et al., *supra* note 7 (studying the rise of Twitter and Facebook as new sources).

125 *See* FDA, *Mining Social Media for Adverse Event Surveillance*, *supra* note 48.

126 *See id.*; *see also, e.g.,* FDA, *Clarification on Using Wood Shelving in Artisanal Cheesemaking, supra* note 25 (withdrawing previous informal statements that the FDA would prohibit longstanding practice of aging cheese on wooden boards).

127 Cortez, *supra* note 44, at 1376.

128 *Id.* at 1376, 1428.

E. Emergency Taskforce

An emergency task force will be extremely helpful at quickly responding to products like the LPM, which are already on the market and potentially harming the public. In such cases, the FDA cannot take five months or more to reach a conclusion.[129] Adverse publicity here is simply not enough, even if it may scare up conversation between patients and their healthcare providers. Because the FDA is the leading regulator of such products, it should also be the leader in the conversation as to how to approach the products.[130] As Dr. Reed pointed out in the LPM case, if the FDA fails to offer answers, it violates its duty to protect the public from potentially harmful and unsafe products.[131] An emergency taskforce can aid in the FDA's protection of the public by utilizing available information and conducting additional field research to determine whether an immediate response for a recall is required.

V. APPLICATION OF THESE RECOMMENDATIONS TO THE LPM CRISIS

In lieu of the second press release's resolution, the recommended amendments to FDA's use of publicity can be applied to the LPM crisis. The recommendations offer more effective and possibly less panic arousing public health communication methods to an agency committed to protecting consumers through the regulation of food, drugs, cosmetics, and medical devices.

A. Research

The FDA's first press release regarding the LPM did not offer any definitive conclusions, but merely suggested the LPM posed a "risk" that could worsen patients' survival.[132] The harmful effects of LPM became more apparent after testimony surfaced in the FDA committee meetings with the Obstetrics and Gynecology Devices Panel and the subsequent FBI Investigation.[133]

The FDA admitted that there was little research on whether the LPM caused the later development of uterine sarcomas. The FDA should have thought further, and recognized that eight studies and one abstract were not conclusive enough to announce that 1 in 350 women relying on the LPM would later develop cancer.[134] Relying on a small number of studies and issuing a press release about a substantial public health issue may indicate that the lack of substantiation by the FDA caused the FDA to breach its duty to the public, or at least that there was a great deal of information left unturned.[135] By increasing the minimum threshold requirement for research studies cited, the FDA could have had the support of more doctors and hospitals to support its position and

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129 *See* Levitz, *supra* note 74.

130 21 U.S.C. § 353 (2014); Levitz, *supra* note 74.

131 Levitz, *supra* note 74 (highlighting the FDA's duty to support and protect the American consumer by diligently approving products that are healthy and safe to use but also providing professional users of such devices with due instructions on best performance practices).

132 FDA, *April 2014 Press Release*, *supra* note 60.

133 *Id.*; Levitz, *supra* note 83.

134 FDA, *April 2014 Press Release*, *supra* note 60.

135 *Id.*

dissuade the use of the medical device. If the FDA utilized dissemination channels with direct access to patients: doctors, hospitals, and manufacturers, consumers would have been immediately informed and dissuaded against the use of the medical device.

B. Due Notice

Notice would be a more difficult concept to tackle here simply because the medical device industry under the regulation of the FDA is quite unlike the other consumer products regulated by the FDA in that the product is not available to the everyday consumer. However, if the FDA had given notice to both the manufacturers of the surgical medical device and the hospitals and doctors who used them, then there might have been a greater consolidation of the opinions regarding the medical device and furthermore, a better understanding of how to properly treat patients with or without it. There currently exists too much lag time between when information is available about when a device is unsafe and when the FDA issues a public determination that a device is unsafe.[136] Had the FDA notified device manufacturers, doctors, and hospitals earlier that it was committed to further researching ill health effects, there could have been a greater collaboration amongst everyone instead of the blowback the FDA received after issuing the press release. Although LPM was life-threatening, in a less dangerous context, both notification of industry personnel and consultation with experts provide stronger basis for the FDA to release adverse publicity. By collaborating its efforts, the FDA not only decreases the hostility the industry feels toward the agency, but it also increases the likelihood for voluntary participation in its device program effectiveness efforts.

C. Emergency Taskforce

The LPM is also a prime example of products already on the market potentially causing harm, which the FDA should investigate quickly. The FDA should not have taken nearly five months to report its advisory committee's findings in its second press release. The delay justifies distrust of the FDA as it currently operates and questions about whether the FDA is truly doing its best to protect the public welfare. If the FDA had an emergency taskforce when this crisis arose, it could have acted more quickly.

CONCLUSION

While the FDA is tasked with protecting the health of consumers by regulating products in the marketplace, its authority for use of publicity should be limited.[137] At the very least, the FDA must exercise care and minimize unnecessary harm to manufacturers and consumers.[138] This is particularly important as the FDA increasingly relies on adverse publicity to warn the public of *potentially* harmful products and threaten manufacturers to recall those products voluntarily.[139]

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[136] *See* Levitz, *supra* note 83.

[137] 21 U.S.C. §§ 379f-j62 (2012) (extending user-fee programs for prescription and medical devices, establishing user-fee programs for generic drugs and biosimilars, but that requiring inspection of drug manufacturing facilities, domestically and abroad based on risk assessment factors).

[138] *See* Gellhorn, *supra* note 4.

[139] FDA Enforcement Statistics, *supra* note 12.

Adverse publicity often creates the burden of stress for consumers, especially when a press release is later proven untrue or misrepresented. When consumers panic or fail to adequately understand FDA warnings, manufacturers suffer economically. Therefore, the FDA must gather adequate data and provide notice to manufacturers before issuing a press release containing adverse publicity. The FDA should also exhibit self-restraint on what to put into the media stream and be prepared to issue corrective statements and retractions in the case of false or misleading information. Congress can mandate these improvements by amending the FDCA or the APA, or the FDA can voluntarily implement these improvements.

Combined, these changes would improve the FDA's ability to make public statements that effectively protect consumers from dangerous products without unduly punishing manufacturers with unreasoned adverse publicity. If the FDA conducts proper research and utilizes its resources, the next time a product raises immediate concern, the FDA will be able to expeditiously address the issue, keep consumers informed, and strengthen its relationship with regulated entities.

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