When Worlds Collide: Drugs and Devices

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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

\(^2\) 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.” These help health care providers determine the risks and benefits of a particular drug for a patient. 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.

In addition to companion diagnostics, the FDA states that combination products also fall under the personalized medicine umbrella. 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. 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. 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. With the help of personalized medicine, health care management can focus more on wellness and maintaining health, rather than on illness and treating disease. 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.

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 on how the FDA evaluates combination products and the various ways companies can develop them under current regulatory and economic obstacles.
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.

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21 FDA, About Combination Products, http://www.fda.gov/CombinationProducts/AboutCombinationProducts/default.htm.
22 Id.
23 Id.
24 Id.
26 Id.
to achieve their intended purpose.\textsuperscript{27} Therefore, the statutory requirements for device marketing approval applications are slightly easier to meet.\textsuperscript{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\textsuperscript{29}, manufacturing and quality control, adverse event reporting, promotion and advertising\textsuperscript{30}, and post-approval modifications\textsuperscript{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.\textsuperscript{33} Congress made this requirement because of the challenges of combination products from patient, medical, and legal perspectives.\textsuperscript{34}

On December 24, 2002, FDA established OCP and gave it several responsibilities.\textsuperscript{35} First, OCP serves as a focal point for combination product issues for agency reviewers and industry.\textsuperscript{36} Second, OCP develops guidance and regulations to clarify the regulation of combination products.\textsuperscript{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.\textsuperscript{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.\textsuperscript{39} Fifth, OCP ensures consistency and appropriateness of post-market regulation of combination products.\textsuperscript{40} Sixth, OCP resolves disputes regarding the timeliness of premarket review of

\textsuperscript{27} Id.

\textsuperscript{28} Id. (explaining the differing regulatory requirements for drugs and devices in further detail).

\textsuperscript{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).

\textsuperscript{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.

\textsuperscript{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.

\textsuperscript{32} Id.


\textsuperscript{34} FDA, Transcript of Public Hearing on FDA Regulation of Combination Products, http://www.fda.gov/downloads/CombinationProducts/MeetingsConferencesWorkshops/UCM117123.pdf.

\textsuperscript{35} FDA, Office of Combination Products, http://www.fda.gov/AboutFDA/AboutCentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018184.htm.

\textsuperscript{36} Id.

\textsuperscript{37} Id.

\textsuperscript{38} Id.

\textsuperscript{39} Id.

\textsuperscript{40} Id.
combination products. Seventh, OCP updates agreements, guidance documents, and practices specific to the assignment of combination products. Finally, OCP submits annual reports to Congress on the Office’s activities and impacts.

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”). 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. “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. 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.” 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.” 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.” 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.

The FDA determines the PMOA by looking at previously approved products or through case-by-case analysis. For some types of combination products, the constituent part that contributes the PMOA is well established. 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. To illustrate, a drug in a prefilled syringe would be considered to provide the PMOA. 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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{60} If so, the product is assigned to that center.\textsuperscript{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.\textsuperscript{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.\textsuperscript{63} An RFD requests a determination of which FDA center will have primary jurisdiction for premarket review and regulation of a combination product.\textsuperscript{64} A product’s sponsor must submit an RFD before filing any investigational or marketing application for the product.\textsuperscript{65} A RFD includes (1) the identity of the sponsor; (2) a description of the

\begin{footnotesize}
\textsuperscript{55} Id. at 364-65.
\textsuperscript{56} Id. at 365.
\textsuperscript{57} Id.
\textsuperscript{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 is made.” See Definition of Primary Mode of Action of a Combination Product, supra note 46.
\textsuperscript{59} Id.
\textsuperscript{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).
\textsuperscript{61} Weiner, supra note 16 at 365.
\textsuperscript{62} Id.
\textsuperscript{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.
\textsuperscript{65} Id. at 4.
\end{footnotesize}
product\textsuperscript{66}; and (3) the sponsor's recommendation as to which Agency center should have primary jurisdiction.\textsuperscript{67} Within 5 days of receiving a RFD, OCP must review the submission for completeness and determine whether the RFD contains the required information.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{71} A request for reconsideration cannot exceed 5 pages and cannot include any new information that was not contained in the original RFD.\textsuperscript{72} The FDA must then review and give a response to the sponsor within 15 calendar days of receipt of the request for reconsideration.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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

\textsuperscript{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).

\textsuperscript{67} Id. at 6-7; see also 21 C.F.R. § 3.7(c)(2015).

\textsuperscript{68} § 3.8(a).

\textsuperscript{69} FDA, \textit{Guidance for Industry: How to Write a Request for Designation (RFD)}, supra note 64 at 5.

\textsuperscript{70} Id.

\textsuperscript{71} § 3.8(c).

\textsuperscript{72} Id.

\textsuperscript{73} FDA, \textit{Guidance for Industry: How to Write a Request for Designation (RFD)}, supra note 69 at 5.

\textsuperscript{74} Id.

\textsuperscript{75} Id. at 3-4.

\textsuperscript{76} Weiner, \textit{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. 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. 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. Furthermore, the PMOA standard does not establish how the lead and non-lead centers should coordinate or how sponsors should interact with either. However, statutory language and agency policies, statements, and practice offer insight into these questions. 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. However, CDER, CBER, and CDRH do not currently have the delegated authority to review all marketing application types. Specifically, CDER has the authority to review some biologics licensing applications (BLAs), new drug applications (NDAs), abbreviated NDAs (ANDAs), and investigational new drug applications (INDs). CDRH has the authority to review Premarket Approvals (PMAs), 510(k)s, Humanitarian Device Exceptions (HDEs), and Investigational Device Exemptions (IDEs). Finally, CBER has the authority to review all of these types of submissions. 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.
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

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. However, abbreviated marketing authorizations would be available to allow follow-on applicants to be on the market once such exclusivities expire. 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. Finally, if a product is marketed under a PMA, there is a six-year data exclusivity provision. 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. 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. 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. 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. Furthermore, the FDA has indicated that a marketing authorization must also consider questions of safety and efficacy that arise when constituent parts are combined. To meet these requirements, experts from several offices must work together to evaluate the combination product.

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.


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. Combination products often require complex inter-center coordination and interaction in order to facilitate premarket review.

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. 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). OCP sends annual reports to Congress and these include data tracking of the number of consults between centers.

Sponsors coordinate with the FDA through the lead center. 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. OCP facilitates scheduling of meetings and coordinates other matters between the sponsor and the FDA. Furthermore, OCP helps resolve disputes regarding product review.

Good relationships between sponsors and manufacturers of different types of products can further support product review and the approval process. For example, if a drug sponsor and a device manufacturer are developing a product together, their relationship can benefit the approval process. 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. 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. 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. 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. 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. OCP aimed to ensure that these regulatory requirements were met and to minimize any unnecessary overlap.

Combination products require coordination across centers and other agency offices during post-market regulatory activity. 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. OCP assists in that coordination so that combination products are in compliance with all regulatory requirements and can maintain their presence on the market.

F. Disputes over the OCP’s Center Assignment

Generally, OCP has worked well with combination product sponsors; however, one case, _Prevor v. FDA_, 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. Prevor argued that the product’s PMOA came from its device constituent part. However, the FDA stated that DSW had a drug PMOA, and Prevor challenged this determination.

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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. It is a liquid substance that is contained in a canister propelled by pressurized gas. The liquid substance is colorless and odorless and is 96% water and 4% diphoterine. 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).” The FDA stated that if the product depends “at least in part” on any chemical action, then it is automatically not a device. 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.” Specifically, Prevor claimed that the FDA incorrectly applied the FDCA’s definition of a device. 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.” Prevor disagreed with the FDA’s conclusion that DSW has more than one primary intended purpose. Specifically, Prevor stated that the neutralization of chemicals is not one of DSW’s primary intended purposes.

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.” 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. The court remanded the case to allow the agency to make a determination consistent with the holdings in its opinion.

On remand, the FDA reached the same conclusion that DSW was a drug, yet with one difference. The FDA found that DSW had only one primary purpose: “to help prevent and minimize accidental chemical burn injuries.” Prevor argued against a
second remand back to the FDA. 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. Prevor and the FDA both filed Motions for Summary Judgment.

On September 9, 2014, the U.S. District Court for the District of Columbia rejected Prevor’s argument and denied the FDA’s motion. The court held that in selecting one primary purpose alone, the FDA conveniently avoided distinguishing between primary and secondary purposes. 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.” The court implied that the FDA’s definition of “achieve” as “chemical action [that] meaningfully contributes to its primary intended purpose” was creative. Unlike the FDA, the court did not find that “achieve” means “meaningfully contribute.” 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.” 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. The court noted that this language does not appear in legislative history, any FDA guidelines, or in any other classification decisions. While the FDA is allowed to adopt new approaches, it must offer a reasonable analysis for its new approach. 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.” 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. 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

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.
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.” However, the court found that the record showed that FDA’s classification decision was based on “erroneous and unreasonable interpretation of the law.” For these reasons, the court remanded the case back to the FDA for further proceedings consistent with its opinion.

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, demonstrated that the industry may benefit from further insight into the FDA’s thought process in interpreting a PMOA. Second, the FDA’s interpretation of chemical action under Section 201(h) of FDCA is unclear and also warrants further insight. Still, despite the potential benefits of more guidance, the industry already benefits from the OCP.

G. Benefits of OCP

Despite , 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.” The states that since its establishment, the OCP has served as an important resource to manufacturers. CPC states that OCP “consistently helps manufacturers navigate the murky and sometimes stormy waters created by the cross-center regulation of their products.” Most notably, CPC praises OCP for “getting” some of the highest marks of any office at FDA when it comes to responding quickly to pleas for help.” 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.” 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. 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.
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.\textsuperscript{177} CPC remembers the regulation of combination products before OCP existed and believes the industry is “lucky” to have OCP.\textsuperscript{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.\textsuperscript{179} The devices test to see whether a drug or biologic’s benefits outweigh its risks for a particular patient.\textsuperscript{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.\textsuperscript{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.\textsuperscript{182} At the time of this article’s publication, only about twenty companion diagnostics have been approved.\textsuperscript{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).\textsuperscript{184} OIR is comprised of the Office of the Director, which includes the personalized medicine staff and seven divisions.\textsuperscript{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.\textsuperscript{186} To foster innovation,

\begin{itemize}
\item \textsuperscript{177} Id.
\item \textsuperscript{178} Id.
\item \textsuperscript{179} FDA, \textit{Companion Diagnostics}, http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm407297.htm.
\item \textsuperscript{180} Id.
\item \textsuperscript{182} Id.
\item \textsuperscript{183} FDA, \textit{List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)}, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.
\item \textsuperscript{184} FDA, \textit{Office of In Vitro Diagnostics and Radiological Health}, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm115904.htm.
\item \textsuperscript{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).
\item \textsuperscript{186} Id.
\end{itemize}
OIR combines pre-market and post-market responsibilities into one multi-disciplinary office. Additionally, OIR administers the federal Clinical Laboratory Improvement Amendments (CLIA). 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.

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. 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. 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. 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.

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). This is because the FDA stated that it intends to require separate marketing applications for a therapeutic product and a companion diagnostic device,
regardless of whether the products could constitute a combination product.\textsuperscript{196} However, the FDA stated that the standards for review, approval or clearance would be the same.\textsuperscript{197}

1. Timeline
The FDA stated that ideally, a therapeutic product and its companion diagnostic will be developed and cleared contemporaneously.\textsuperscript{198} However, the FDA recognized that there may be cases when contemporaneous development is not possible.\textsuperscript{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.\textsuperscript{200}

2. Review And Approval
In the guidance document, the FDA said that it reviews companion diagnostics and therapeutic products under applicable regulatory requirements.\textsuperscript{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.\textsuperscript{202} The FDA aims to review each companion diagnostic device application within the context of its corresponding therapeutic product.\textsuperscript{203} The FDA stated that when a new therapeutic product requires a companion diagnostic to be safe and effective, the two products should be developed and approved contemporaneously.\textsuperscript{204} Before approving a therapeutic product, the FDA will make sure that the companion diagnostic device meets the applicable standard for safety and effectiveness.\textsuperscript{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.\textsuperscript{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.\textsuperscript{207} The FDA noted that in such situations, it expects that the companion diagnostic device will be subsequently approved.\textsuperscript{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

\begin{itemize}
\item \textsuperscript{196} \textit{Id.}; see also 21 C.F.R. § 3.4(c) (2015).
\item \textsuperscript{197} FDA, \textit{In Vitro Companion Diagnostic Devices, supra} note 189.
\item \textsuperscript{198} \textit{Id.} at 7.
\item \textsuperscript{199} \textit{Id.}
\item \textsuperscript{200} \textit{Id.}
\item \textsuperscript{201} \textit{Id.}
\item \textsuperscript{202} \textit{Id.}
\item \textsuperscript{203} \textit{Id.}
\item \textsuperscript{204} \textit{Id.}
\item \textsuperscript{205} \textit{Id.}
\item \textsuperscript{206} \textit{Id.}
\item \textsuperscript{207} \textit{Id.} at 9.
\item \textsuperscript{208} \textit{Id.}
\end{itemize}
benefits outweigh the risks. 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. 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. 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. The FDA emphasized that it generally will determine that a serious safety issue exists before approving a supplement to an approved therapeutic product application.

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. 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. The FDA emphasized that it generally will determine that a serious safety issue exists before approving a supplement to an approved therapeutic product application. 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. 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. 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. Therefore, the level of risk will establish whether a companion diagnostic requires a PMA or a 510(k).

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.

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.

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. Although this guidance gives industry some insight into the FDA's processes, industry is still unable to find answers to all of its questions.

209 Id.
210 Id.
211 Id.
212 Id.
213 Id.
214 Id.
215 Id. at 10.
216 Id.
217 Id.
218 Id. at 10.
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. 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. 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.

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. 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. This would allow companion diagnostics and their corresponding therapeutic products to be developed more quickly, which would benefit all stakeholders.

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. While OCP has not yet resolved certain issues, it has been tremendously helpful to the world of combination products. 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. While

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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. 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. 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.

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. 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. The CBO will recommend a certain amount of Congressional appropriations necessary for the office. 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.

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

MDUFMA provides more limited user fee waiver options than PDUFA provides. Under MDUFMA, almost every sponsor must pay the same standard fee upon submitting a device application. 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. A small business pays 38% of the standard PMA and BLA fee and 80% of the standard 501(k) fee. MDUFMA also provides a one-time waiver for the first premarket application from a qualified small business. As MDUFMA applies to combination products, it would likewise apply to companion diagnostics.

PDUFA offers more options for user fee waivers. PDUFA offers a waiver for the first human drug application from a small business. However, PDUFA defines a small business differently than MDUFMA. Under PDUFA, a small business is one that has fewer than 500 employees for its business and affiliates. 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. Furthermore,
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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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. 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. The FDA notes that the existence of a treatment alternative would weigh against deciding that a product is innovative.

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. 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. Congress should consider these challenges and potential benefits, and create a special waiver for companion diagnostics like the Innovative Combination Product Waiver. 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. 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. Another option is to give companion diagnostics and their therapeutic products priority or accelerated review. 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.
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.
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. 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.

Second, experts from CBER or CDER and CDRH should meet to discuss the data that is submitted with each application for each product. As companion diagnostics will determine how best to administer their corresponding products, there will be some overlap of data submitted with their applications. 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. 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

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


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. 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. Device classifications depend on the claimed intended use and the indications of the device. 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. 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. 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. Companion diagnostics have been subject to Class III designations, and will likely continue to be.

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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. Furthermore, most companion diagnostics will not have a predicate device to cite in a 510(k) submission. Notably, companion diagnostics approved through the PMA process may be eligible for a patent term extension.

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.

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. 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. 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. While drugs, biologics, and devices have traditionally been independently regulated,
they are becoming more and more intertwined.\textsuperscript{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.”\textsuperscript{290}

\textsuperscript{289} Combination Products Coalition, Op Ed, supra note 170.