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FDA and Product Jurisdiction: Time for Reforms

By Jeffrey N. Gibbs

How a therapeutic product is classified profoundly affects how that product is regulated. The Food and Drug Administration (FDA) regulatory process is inextricably linked to product classification. A product regulated as a device has a very different path to the market than the same product if it is regulated as a drug or biologic.

Product classification is ultimately dichotomous. A product will either be regulated as a device or pharmaceutical. For combination products, the same principle holds; there will be one lead FDA Center, applying either device or drug/biologic requirements. The time to market, the regulatory requirements to get there, regulatory costs, and the post-market regulatory obligations will all be shaped by which Center plays that lead role. Given that FDA received approximately 300 combination product submissions in 2013, the agency's product classification policies affect many products.[1]

Unfortunately, the mechanism for classifying products is increasingly challenging and fraught. There are two primary problems. First, the substantive criteria used by FDA to classify products have evolved in ways that push more products into the pharmaceutical realm. Second, the process by which FDA makes its decisions has become less transparent and less predictable. This article will discuss these two aspects of the process for determining jurisdiction.

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Background

The basic legal problem underlying therapeutic product classification is that the statutory definitions of drugs and devices are so similar. The term "drug" is defined, in pertinent part, as

> (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified [above]."[2]

A device is defined in exactly the same way, except that the device definition is further restricted to only an article

> which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."[3]

This restriction—the so-called "exclusionary clause"—was added by Congress in 1976 when it enacted the Medical Device Amendments and amended by the Safe Medical Device Amendments of 1990. In 1976, Congress stated that its intention was to "draw a clear distinction between a 'device' and a 'drug'" and "remove[] the gray area that exists between the definitions."[4] Subsequent events have shown Congress did not achieve these goals.

Although products that combined drugs and device components existed in 1976, they were less common than today. Congress did not focus on this aspect in crafting the drug and device definitions. Over time, it became apparent that FDA needed criteria for classifying combination products. Thus, when Congress passed the Safe Medical Devices Act of 1990, it directed FDA to designate lead centers within the agency to "regulate products that constitute a combination of a drug, device, or biological product."[5] The Act further stated that

> The Secretary shall determine the primary mode of action of the combination product. If the Secretary determines that the primary mode of action is that of – (A) a drug (other than a biological product), the agency center charged with premarket review of drugs shall have primary jurisdiction; [or] (B) a device, the agency center charged with premarket review of devices shall have primary jurisdiction[.][6]

FDA was required to promulgate regulations implementing these provisions.[7]

Accordingly, in 1991, FDA adopted regulations addressing combination products.[8] FDA's regulations broadly addressed combination products, and clarified that a product could be deemed a combination product by physically combining a device and drug, through cross-reference labeling, i.e., the drug labeling referencing the device or vice versa, or by packaging a drug together with a device.[9] These regulations helped to clarify *what* constituted a combination product, but not *how* that product would be regulated. The regulations did not further define the statutory term "primary mode of action," or "mode of action."

FDA's regulations relied on a series of Intercenter Agreements in effect between the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Center for Drug Evaluation and Research (CDER). These were agreements between the Centers assigning primary jurisdiction to Centers for enumerated products. While initially useful, these documents have become less relevant over time as new combination products have been introduced and, perhaps more important, FDA's views have changed. Although the Intercenter Agreements remain in effect, FDA cautions that they "should not be independently relied upon as the agency's most current, complete jurisdictional statements."[10] That is good advice.

As the number of jurisdictional issues and their complexity grew, FDA faced another question: who would decide these jurisdictional issues? Initially, the decisions were made by the FDA Ombudsman. In 2002, Congress mandated the creation of a separate office to make jurisdictional decisions,[11] and FDA established the Office of Combination Products (OCP) on December 24, 2002.

Finally, in 2005, FDA published additional combination product regulations, which defined two key terms: "mode of action" and "primary mode of action."[12] FDA also set forth an algorithm to govern classification decisions where the Agency cannot determine with reasonable certainty which mode of action is primary.[13] In those cases, the regulations state that the product will be assigned to the agency component that regulates other combination products that present similar safety and effectiveness questions.[14] The final tiebreaker in the algorithm, where FDA can identify no other combination products that present similar questions of safety and effectiveness, is that the product will be assigned to the agency component "with the most expertise related to the most significant safety and effectiveness questions presented by the combination product."[15]

Congress set a 60-day deadline for OCP to reach a product classification

and jurisdictional decision.[16] If OCP does not decide within 60 days, then the applicant's recommendation as to product classification is deemed accepted.[17] The provision has ensured that OCP does, in fact, issue timely decisions.

Congress and FDA regulations also established a procedure for obtaining binding rulings,[18] called a Request for Designation (RFD). FDA's regulations specify the content of an RFD, including the identity of the product sponsor and a description of the product; the classification and name of the product and all components in the US; the chemical, physical, or biological composition of the product, status and reports of any developmental testing; a description of the manufacturing processes and sources of all components; the product's proposed use or indication; a description of all known modes of action; the dose and route of administration if applicable; a description of related products, and any other relevant information.[19] RFD's must also contain the product sponsor's (1) identification of the single mode of action that provides the most important therapeutic action of the product, and the basis for that determination, and (2) recommendation as to which agency center should have primary jurisdiction over the product.[20] Despite its substantial content requirements, RFDs are limited to 15 pages.

Thus by 2005, the basic framework we have today was in place. The key statutory definitions were set in 1976 and 1990, supplemented by FDA's Intercenter Agreements (which nominally remain in place, but are not authoritative) and FDA's regulations for determining whether a product is a combination product, and which agency component should regulate it.

Current Classification Issues

More recently, there has been increasing concern with the product jurisdictional process. These concerns relate to two different aspects: substantive and procedural.

First, FDA has changed its classification criteria in a manner that favors drug classifications. This is evident both in the draft guidance documents proposed in 2011, and in the Prevor litigation discussed below.

Second, FDA has changed its procedure for how it handles RFDs, often without public notice or explanation. For example, OCP has imposed a "Refuse to Accept" policy without publicly announcing the policy or its contents. OCP has also implemented an "Informal RFD" process, without explaining to applicants the pros and cons of this process or articulating how it functions.

Device vs. Drug

Ultimately, a product can have only one lead Center. Thus, FDA must make an either/or decision. However, combination products, by definition, do not easily fit into one category or the other. And single component products that are presented to OCP would typically have dual mechanisms; if not, they would be unlikely to be the subject of an RFD. This tension is at the heart of the classification challenge: a product that has both device and drug characteristics must be placed into one category or the other.

It is difficult to know what proportion of RFDs request device status. OCP does not publicize these data. In the authors' experience, attaining device classification or CDRH primary jurisdiction is the goal of most RFDs. In response to a congressional inquiry in 2012, FDA noted that it is unable to disclose information about many classification decisions, because "classification decisions for investigational products remain confidential until such time as the product at issue receives marketing authorization."[21]

Under section 201(h)(3) of the Food, Drug, and Cosmetic Act (FDCA), a product is not a device if it "achieve[s] its primary intended purposes through chemical action within or on the body of man." While Congress may have believed the meaning of this "exclusionary clause" to be self-evident, it is not.

First, what does the word "achieve" mean? Put another way, what is the level of chemical action at which the product loses its device status? Second, what exactly, is "chemical action"?

From 1976 to 2011, there was no public attempt by FDA to articulate criteria for addressing either issue. Then, FDA issued two draft guidances: Classification of Products as Drugs and Devices and Additional Product Classification Issues, (Draft Classification Guidance), and Interpretation of the Term "Chemical Action" in the Definition of Device under Section 201(h) of the FDCA (Draft Chemical Action Guidance).

In its Draft Classification Guidance, FDA proposed a low threshold for what "achieve" meant. FDA stated that "a product that depends, even in part, on chemical action within or on the

body of man to achieve any one of its primary intended purposes, would not be a device."[22] Any therapeutic effect of the product would be considered a primary intended purpose.[23] Thus, FDA was basically applying a "but for" type of test.

At about the same time as the release of the draft guidance, a French company, Prevor, submitted an RFD for a product used to treat skin exposed to chemicals. The product consisted of a liquid that was comprised of approximately 96% water and 4% of a chemical called diphoterine. The liquid was sprayed on the skin, washing away the harmful chemical. Prevor's data, which FDA disputed, showed that approximately 90% of the effect of the product was due to physical action. OCP classified the product as a drug. In doing so, OCP said a product was a drug if it achieved its primary intended purposes, "at least in part," through chemical action. Prevor appealed, and the Office of Special Medical Products (OSMP) upheld the decision using similar criteria as OCP, stating that a product is a drug if it "depends, even in part, on chemical action within or on the body to achieve any of its primary intended purposes." Prevor appealed that decision. Judge Rosemary Collyer reversed FDA's decision, finding that the agency's "at least in part" or "even in part" analysis with respect to primary intended purposes was a new interpretation of the device definition that FDA had failed to adequately explain. The decision went on to state that "without such an interpretation of 'primary intended purpose,' DSW [Prevor's product] could be designated a 'device.'" She remanded the matter to FDA.

On remand, OSMP again found DSW to be a drug. OSMP applied a "meaningfully contributes" test. Again Prevor sued, and again Judge Collyer remanded, finding that the word "achieve" in the statute unambiguously required more than that chemical action "meaningfully contributes" to a primary intended purpose. After the remand, OSMP again found DSW to be a drug, purporting to directly apply the statutory language rather than offer any new interpretation; Prevor did not appeal that decision. OSMP drew heavily on promotional materials published by Prevor outside the United States to support its decision.

The Prevor litigation establishes that the word "achieves" means neither "in any part" nor "meaningfully contributes." It is still far from clear, though, what the word *does* mean. On remand, OSMP found that DSW "achieved" its effect through chemical means, without defining that term. There is also the issue of the appropriate burden of proof sponsors must meet to support their recommendation; OCP has applied a "reasonable certainty" standard to the data submitted by the applicant.

As for combination products, the meaning of "primary mode of action" has become less certain. It had appeared that if the available data showed that the preponderance of the therapeutic effect was due to the device, then the product would be regulated by CDRH. However, it does not appear that OCP is using a straightforward mathematical model. That is, showing that the device contributes over 50% of the effect may not be sufficient. Consider, for example, a hypothetical product that is labeled as effective for one month. Consider further that the drug is shown to be primarily responsible for the first three days of effect, and the device mode of action predominates for 25 days. While it might seem evident that the device mode of action is primary absent a reason to overweight the drug contribution of the first three days—it is the major source of therapeutic effect for 25 of 28 days—receiving a device designation by FDA is far from certain.

In addition, OCP has asked companies to conduct rigorous studies with statistically robust methodologies to calculate the relative effect. There is a practical problem: How can a company conduct a complex study and then squeeze in all the necessary data—plus other information—in 15 pages? Even more fundamentally, though, there are no pre-defined criteria as to what would constitute sufficient evidence to support device classification.

Procedural Issues

In addition to the substantive issues discussed above, the RFD process presents several procedural issues. These can affect both the outcome of the designation process and the manner in which applicants view the process.

One peculiar feature of the RFD process is that there is a page limit. By regulation, RFDs cannot exceed 15 pages. Thus, RFDs are similar to briefs in court and term papers, but unlike other FDA submissions.

It is not clear how or why the page limit was instituted, but it appears to be unique to RFDs. In other settings, applicants can be as prolix as they wish. Given the importance of product jurisdictional determinations, it cannot be linked to significance. And

given the complexity of many RFDs, it cannot stem from a belief that these matters are so simple that 15 pages is always enough. Given the tight space limits, it is also unclear why some information that typically has little relevance to jurisdictional decisions, such as manufacturing process, is requested. As OCP's requests for data have grown, the 15-page limit has become even more of a relic. FDA should reconsider this arbitrary limitation.

Another procedural issue is of newer vintage: OCP's refusal to accept RFDs. OCP will now refuse to file RFDs. OCP started this program without public notification. OCP has provided no criteria for when it will refuse to file an RFD, leaving applicants in the dark.

OCP's approach here is in stark contrast to CDRH's recent adoption of a refuse to accept program for 510(k) premarket notifications. CDRH first issued a draft guidance document, which described the proposal in detail, explaining how the process would work and the criteria employed in reviewing submissions.[24] OCP's policy is a black box, giving applicants no insight into how OCP decides when to reject a submission.

There is nothing inherently problematic with FDA implementing a refuse to accept policy for RFDs. CDRH has these program policies for premarket approval applications,[25] and 510(k)s. CDER retains the authority to refuse to file new drug applications and refuse to receive abbreviated new drug applications.[26] It is troubling, though, for a component of FDA to implement its own refuse to file policy without public notice, let alone providing an opportunity to comment on this new program.

OCP has adopted a mechanism, by which companies can, at least indirectly, submit more than 15 pages for the informal submission. It is not clear when this program went into effect; however, OCP is now suggesting to potential applicants that they file an "informal RFD."

There can be advantages to this approach. For example, because this is not an RFD, it is apparently not subject to the 15-page restriction. Given that it is a tool to receive informal feedback, the informal RFD should not have to pass a threshold for reviewability. OCP has also advised companies that this process would be interactive, unlike the situation with formal RFDs, where the company submits and then awaits a decision. A truly interactive process would be beneficial.

It is not clear, though, whether this latter benefit will actually materialize, i.e., whether OCP will initiate discussions with a company that submits an informal RFD. Nor is it at all clear why OCP could not have interactive reviews for a formal RFD. CDER, CDRH, and CBER routinely discuss applications while they are pending.

The informal RFD does offer another potential advantage to applicants. Given the lack of reliable precedents and OCP's shifting and ill-defined substantive criteria, it is difficult to know what issues a RFD might present. An applicant will learn of OCP's concerns only when OCP issues its decision. At that point, the applicant's only recourses are filing for reconsideration, appealing to OSMP, or potentially, starting litigation.

These options are not appealing. A request for reconsideration is limited to five pages, must be submitted within 15 days of the decision, and is reviewed by the same office as the original decision.[27] Although OSMP is reportedly improving its timeliness, appeals to OSMP can be very slow. In Prevor, OSMP took 13 months to decide the first appeal and eight months after the first remand (reportedly, the time for a decision on appeal has since dropped). In addition, an appeal cannot introduce new scientific evidence, even if needed to address OCP's decision, and even if OCP raised unanticipated issues.

The informal RFD can give an applicant valuable insight into OCP's thinking. If OCP agrees with the applicant's recommendation, then the applicant's path forward is clear: While OCP's feedback to an informal RFD is not binding, presumably OCP would not reverse course if the RFD replicates the information in the informal RFD. Conversely, if OCP disagrees with the recommendation in the informal RFD, that response should enable the applicant to craft its RFD more effectively by knowing OCP's objections.

The intelligence gleaned by an informal RFD will be obtained at the cost of delay. Because it is not a decision but only feedback, akin to CDRH's pre-submission process, an informal RFD decision is not an appealable agency action. While it is possible that the applicant's RFD will persuade OCP to take a different position, if it does not, the company will lose the 60-day period as OCP reviews the RFD and writes its decision. Thus, there is a trade-off: the informal RFD process takes more time but can yield helpful insight.

The jurisdictional review process also lacks adequate transparency.

OCP used to post brief summaries of its decisions.[28] OCP said it was making these decisions available because "transparency in jurisdictional decision making should result in greater predictability and consistency of decisions, and decrease ambiguity and uncertainty about FDA perspectives."[29] However, in 2009 OCP discontinued this practice. OCP does not appear to have publicly explained why it stopped making summaries available; it simply stopped updating the webpage containing the capsular decisions. In contrast, the Tissue Reference Group continues to post summaries of its jurisdictional decisions regarding the regulation of tissue products.[30]

In addition, it is not clear that having precedents would be particularly helpful. OSMP has effectively stated that unless the product has the identical composition and intended use, the agency is not beholden to follow prior outcomes. In the Prevor litigation, FDA dismissed one precedent by saying it would probably reach a different decision if presented with the product today, and dismissed another as "sui generis." This lack of predictability has created issues for companies that expected OCP to follow precedents for closely analogous submissions.

Conclusion

Designation decisions materially affect the regulatory path of products. Although the RFD process can be efficient, it needs to be improved further. Transparency and consistency need to be improved. A more formalized and predictable pre-submission process similar to CDRH's pre-submission meeting program should be established. Beyond procedural reforms, FDA's criteria for making jurisdictional decisions should be reexamined by FDA and Congress. Improving the product jurisdictional process is an area that warrants further review by Congress and FDA.

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1. Combination Product Review InterCenter Consult Process Study (Oct. 14, 2015).
2. 21 U.S.C. § 321(g)(1).
3. 21 U.S.C. § 321(h).
4. H.R. Rep. No. 94-853, at 14
5. Pub. L. No. 101-629, 104 Stat. 4511, 4526 (1990) (codified at 21 U.S.C. § 353(g)).
6. 21 U.S.C. § 353(g)(1).
7. 21 U.S.C. § 353(g)(3).
8. *See* 56 Fed. Reg. 58,754 (Nov. 21, 1991)
9. 21 C.F.R. § 3.2
10. *See* FDA Jurisdictional Update: Intercenter Agreements (September 2006), http://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm106506.htm.
11. *See* Medical Device User Fee and Modernization Act, Pub. L. 107–250, title II, §204 (2002); 21 U.S.C. § 353(g).
12. *See* Final Rule, 70 Fed. Reg. 49,848 (Aug. 25, 2005).
13. *Id.*
14. 21 C.F.R. § 3.4(b).
15. *Id.*
16. 21 U.S.C. § 360bbb-2(b).
17. *Id.* at § 360bbb-2(c).
18. 21 U.S.C. § 360bbb-2(a); 21 C.F.R. § 3.7.
19. 21 C.F.R. § 3.7(c).
20. *Id.*
21. Letter from Michele Mital, Acting Associate Commissioner for Legislation, Food and Drug Administration, to Sen. Johnny Isakson (Dec. 21, 2012) (on file with the author).
22. Draft Classification Guidance, at 4-5.
23. *Id.* at 5.
24. *See* FDA Guidance: Refuse to Accept Policy for 510(k)s (Aug. 4, 2015), at 4-5, *available at* http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm315014.pdf.
25. 21 C.F.R. § 814.42.
26. 21 C.F.R. §§ 314.101(a), (b), (d).
27. 21 C.F.R. § 3.8(c).
28. *See* Capsular Descriptions of Jurisdictional Determinations, http://www.fda.gov/CombinationProducts/JurisdictionalInformation/RFDJurisdictionalDecisions/CapsularDescriptions"One-Liners"/default.htm.
29. *See* RFD Jurisdictional Decisions, http://www.fda.gov/CombinationProducts/JurisdictionalInformation/RFDJurisdictionalDecisions/default.htm.
30. *See* Tissue Reference Group, http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/RegulationofTissues/ucm152857.htm.