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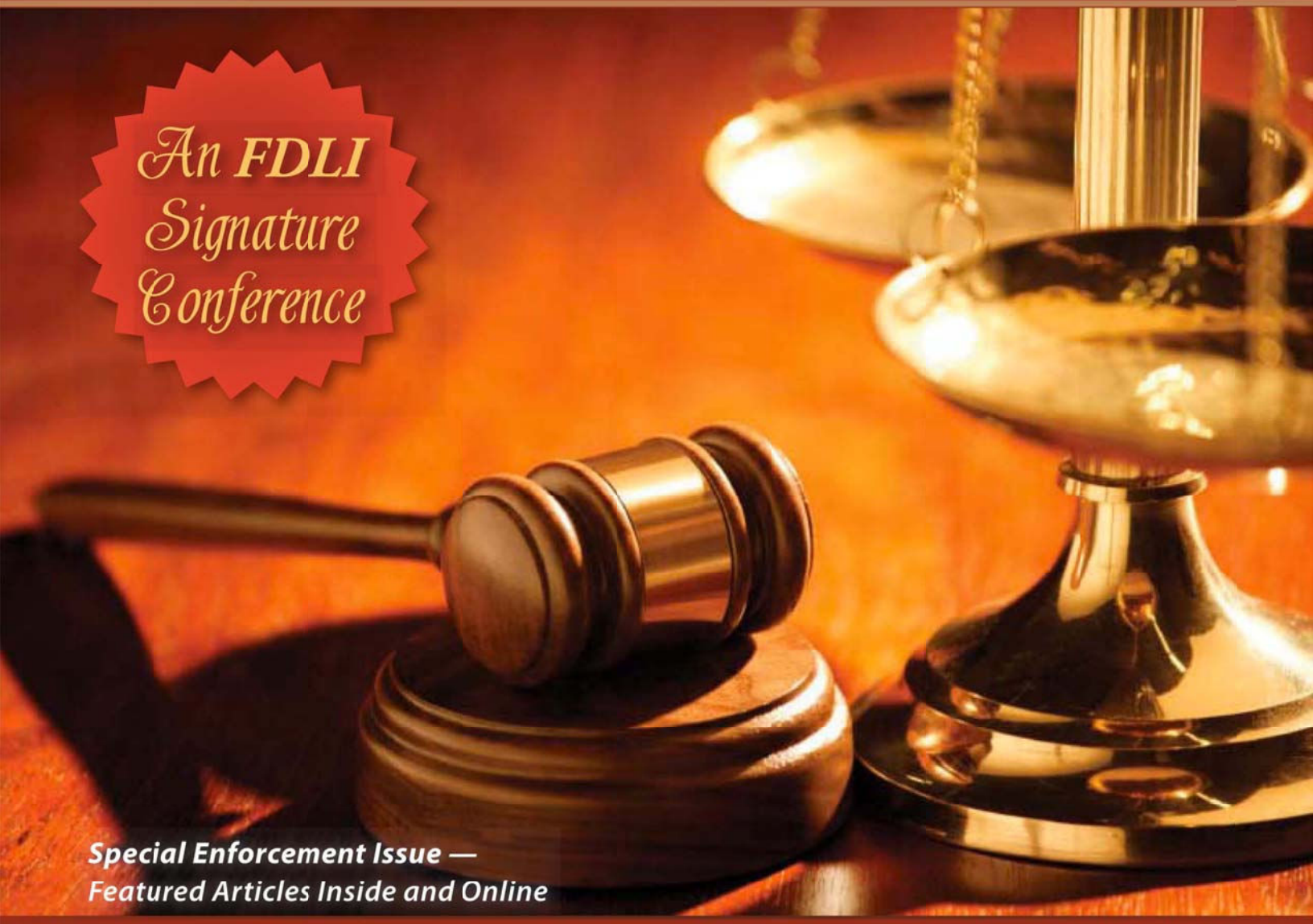

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Two Draft Guidances Seek to Clarify and Potentially Expand FDA Classification of Device and Drug Products — Hidden Risks and Unexpected Benefits

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Introduction

On June 21, 2011, the Food and Drug Administration ("FDA" or the "agency") published two companion draft guidance documents on "Classification of Products as Drugs and Devices & additional Product Classification Issues"[1] and "Interpretation of the Term 'Chemical Action' in the Definition of Device under Section 201(h) of the Federal Food, Drug, and Cosmetic Act."[2] The draft guidances are intended to clarify FDA approaches for determining whether a product will be classified as a drug or device based on application of the statutory definitions for these terms under 201(g) and 201(h) of the Food Drug and Cosmetic Act ("FDCA"). 21 USC 321 (g) and (h).

In addition to describing the process for classification of products, the draft guidances describe the agency's interpretation of the statutory terms, drug and device. Notably, the guidances do not directly address classification of biologics. Special attention is given, however, to the Agency's definition of "chemical action" as it relates to existing and future products, and how this definition should be applied to determine when a product is subject to FDA regulation as a drug or as a medical device. The draft guidances also address the effects of current intercenter agreements and prior agency classifications—i.e., how these guidances affect already marketed products and new products seeking marketing authorization, while also clarifying that the current guidances do not, as of yet, address biological products regulated by FDA pursuant to the Public Health Service Act. 42 U.S.C. §§ 201 et seq.

As explained below, these clarifying guidances appear to provide FDA with greatly expanded flexibility and potentially overbroad discretion in assigning or reassigning existing single entity or combination products as drugs. As currently drafted, they can be read to create *less* certainty as to the regulation of products previously regulated as medical devices. At a minimum, the criteria developed by FDA in these companion documents appear on an initial basis to overlook portions of the existing FDCA statutory language in ways that could have far-reaching and unanticipated effects on medical device and drug manufacturers.

Change in approach to FDA jurisdictional decisions?

A key departure from precedent that FDA appears to be pursuing in these draft guidances comes in the agency's apparent change in the criteria for interpreting the concept of primary mode of action ("PMOA"), upon which jurisdictional decisions for combination products are to be based, as outlined in Section 503(g) of the FDCA.

Specifically, on August 25, 2005,[3] the agency amended the combination product regulations to define mode of action ("MOA") and PMOA. The agency also at that time outlined an algorithm that FDA could use to assign combination products "when the agency cannot determine with reasonable certainty which mode of action provides the most important therapeutic action of the combination product." Per 21 C.F.R. §3.2(k), mode of action is defined as "*the means by which a product achieves an intended therapeutic effect or action…Because combination products are comprised of more than one type of regulated article (biological product, device, or drug), and each constituent part contributes a biological product, device, or drug mode of action, combination products will typically have more than one identifiable mode of action.*" Per 21 C.F.R. §3.2(m), primary mode of action is defined as "*the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to*

make the greatest contribution to the overall intended therapeutic effects of the combination product." The algorithm is codified in 21 C.F.R. §3.4.

The draft "Classification of Products…" guidance proposes changing the agency's approach to resolving multiple MOAs by indicating that the agency will now consider products to have *multiple* primary intended purposes (*e.g.,* each therapeutic effect of the product). Basically, *all* intended effects a product has will be co-primary modes of action. FDA also now suggests that if *any one* of these multiple primary intended purposes is achieved through chemical action within or on the body of man, the product will not be considered a device. Certainly, this approach creates potential for more combination products being regulated as drugs (or biologics) than medical devices, than in the past. However, the proposed approach differs from well-established FDA guidance and practices because it does not seek to establish a single PMOA (where feasible) or balance risks between multiple modes of action by assessing current knowledge about those risks, or by assessing which FDA Center has the greatest experience with these kinds of products. Rather, the proposed guidance suggests that all possible modes of action are primary and, if any of these is remotely chemical in nature, the product should be regulated as a drug.

The companion draft "Chemical Action" guidance also appears to expand FDA's ability to classify or reclassify products as drugs. Specifically, the draft guidance sets forth a number of examples of possible chemical interactions between substances and the body, and describes how these chemical interactions, if they occur within or on the body of man, may exclude a product from regulation as a medical device. Furthermore, although the draft guidance correctly states that "the term 'chemical action' must be read in the context of the statutory definition of 'device' as a whole," the remainder of the guidance focuses narrowly on chemical bonding, while ignoring the statutory language, "and which is not dependent upon being metabolized for the achievement of its primary intended purposes." 21 USC 321(h). Thus, as suggested in the draft guidance, *any* chemical binding between *any* substance in a product with *any* substance in the human body (*e.g.,* infectious organisms), even where such binding acts only to block interaction between the body and the infectious organism, is a drug-related intended effect. By overlooking the clear and unambiguous "and is not dependent on metabolism" language of the statute, the draft guidance suggests that products do not require any relation to metabolic processes to be categorized as drugs. Coupled with the ability to define multiple PMOAs, as laid out in the "Classification of Products…" guidance, and to define as a drug based on any of those PMOAs, the combined result of both guidances, if applied to their extreme, could lead to every substance placed within or on the body being classified as a drug. At the very least, many types of products previously understood to be devices, may now potentially be regulated as drugs.

By way of example, FDA has historically regulated biodegradable sutures and implantable staples, tacks, and screws as medical devices. Many of these products are manufactured using chemicals that bind to and interact chemically with both the bones or muscles into which the products are placed. By their nature, these chemical substances are metabolized by the body as part of their degradation, and the ability of these products to degrade slowly (without needing to be surgically removed) clearly is part of the device's intended effect and indications for use. Under FDA's previous PMOA determination approach, the agency assessed and determined which of all of the possible effects was the primary intended effect and (correctly) determined that the ability of the sutures or staples to hold tissues in their desired location was the PMOA. Since this PMOA is a structural/device intended effect, these products were regulated as medical devices.

Under the draft guidance approach, FDA's well-established PMOA determination process could be turned on its head. Rather than focusing on the primary intended effect of the sutures and screws (*i.e.,* what they actually are intended to do), the agency could focus on the chemical interaction of the products with bone and tissue, or on the chemical process of biodegradation, to determine that *one* of the product's intended effects is chemical in nature. Since one of the device's multiple MOAs is chemical, these products, under FDA's proposed approach, should not be regulated as medical devices. There are hundreds if not thousands of products currently regulated as medical devices, such as surgical meshes of biological origin, natural and synthetic bone void fillers, and coated-metal orthopedic implants, that contain substances that bind to and interact with the human body (many in ways that impact indirectly the safety and effectiveness of the products).

Potential for disparity in product regulation

Whether FDA chooses to apply the rubric of the draft guidances to existing regulated products, or whether (and

to what extent) the agency will create disparity and uncertainty by regulating new products as drugs when existing, virtually identical products are regulated as medical devices, is unclear. But at a minimum the draft guidances appear to create a risk of uncertainty and confusion if they are applied with inconsistency or with too much flexibility.

The agency indicated in the "Classification of Products…" guidance that jurisdictional precedent will no longer be a primary consideration in making future jurisdictional decisions. Specifically, the agency states its intent to approach combination product decisions on a "case-by-case" basis, using "the current state of scientific knowledge". In other words, just because a similar type of product was classified one way in the past, the agency does not intend to necessarily classify it the same way in the future. Certainly, this approach could create disparity in product regulation, if it creates two pathways for "virtually identical" products.[4]

If a single-entity product or component of a combination product falls within an existing classification regulation, the agency indicates it generally intends to classify the product or component within that regulation. However, the agency may also assess whether the classification regulation should be changed (for example, if the agency is now aware that a product currently classified as a device achieves its primary intended purpose through chemical action within or on the body of man). In such a case, the agency will initiate notice and comment rulemaking to implement such a change.

The "Classification of Products…" guidance also appears to indicate that the agency may be looking into options for classifying and transferring products previously classified. Options that are discussed range from exercising enforcement discretion, to revoking approvals for products and requiring new approvals under the new classification. Certainly, such a move could be a significant disruption for manufacturers of existing products in the event that the jurisdiction of their product is changed. Aside from potentially having to pursue a new approval (a new drug application ("NDA") for a product previously cleared under premarket approval ("PMA") or a 510(k) notice, for example), other potential concerns include changes to manufacturing requirements, different patent protection issues, etc.

Finally, in terms of the Intercenter Agreements,[5] the agency indicates it is currently reviewing these documents to determine if they should be modified or replaced.

Regulation as drugs: burdens and opportunities

While presenting risks to device manufacturers and creating potential discontinuity, the draft guidances may offer unexpected opportunities to innovator companies. For FDA's Center for Drug Evaluation and Research ("CDER"), one possible result of the draft guidances would be a potentially significant expansion of jurisdiction. The affected products are likely, therefore, to enjoy both the burdens and the benefits of being regulated as new drugs. But how this is to unfold is murky. It is unclear, for instance, how the Hatch-Waxman Amendments will apply to any products reassigned as drugs under this new approach that were previously regulated as devices. For example, if a product class previously regulated as, say, a class II device subject to the section 510(k) premarket notification pathway must now be approved as a "new" drug, it is unclear to what extent, if any, it could be approved as a safe and effective product based in whole or in part on FDA's prior substantial equivalence determination. And for products previously regulated as devices that now might be regulated as drugs, the prospect of true generic competition is something new.

Ultimately, how this impacts the device space depends on how many and what kinds of products these new draft guidance documents affect. But for new drug products approved under FDCA section 505(b), benefits may include the award of regulatory exclusivity and the rights associated with listing patents in the Orange Book. These rights provide new drug sponsors with a measure of security against follow-on competition. Any subsequent sponsor of an NDA or an abbreviated new drug application ("ANDA") who wishes to rely in some shape or form on the innovator product's approval, will need to respect that product's exclusivity, and will also need to certify that it is not infringing any of the innovator's Orange Book-listed patents (or that those patents are expired or invalid). If within 45 days of receiving notice of that certification, the innovator sues the follow-on applicant for patent infringement, an automatic 30-month stay applies to FDA's approval of the application and can effectively extend the innovator's period of market exclusivity. These can be significant advantages. Moreover, under Hatch-Waxman, to be approved as an ANDA, a generic product must show that it is "the same as" (same active ingredient, same route of administration, same dosage form, same strength, and same labeling) and "bioequivalent to" the reference drug.

As applied to device-like products or components, this can present significant barriers to ANDA approval.

Summary

Importantly, these guidances create industry notice of FDA's apparent intent to liberally determine that a product acts as a drug. This could impact device companies by creating greater ambiguity as to whether existing devices or similar new products will be regulated as devices. If products previously regulated as devices are to be newly rendered as drugs regulated by CDER, the impact could be far reaching. This may be a serious and detrimental development to many device manufacturers – but there may be strategic opportunities related to being regulated under the drug laws that innovator companies may explore.

1. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM258957.pdf.
2. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM259068.pdf.
3. Federal Register Vol. 70, No. 164: 49848- 49862.
4. While the Federal courts in *Bracco Diagnostics, Inc.* (963 F. Supp. 20 (D.D.C. 1997)) agreed with FDA that many products "likely meet both the definition of a drug and the definition of a device" and that "FDA therefore has discretion in determining how to treat them," the Court also held dispositively that "[w]hat the FDA is not free to do, however, is to treat them dissimilarly and to permit two sets of similar products to run down two separate tracks, one more treacherous than the other, for no apparent reason."
5. http://www.fda.gov/CombinationProducts/JurisdictionalInformation/InterCenterAgreements/default.htm.