MI³ Alert

Medical Innovation Impact Index

Initiative for Patient-Centered Innovation

Fairleigh Dickinson University, Silberman College of Business

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General Description of Issue

Combination products are defined as products comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic that are physically, chemically, or otherwise combined or mixed and produced as a single entity. The assignment of the product to the appropriate agency component for regulatory review as either a device, drug, or biologic depends on the determination of the primary mode of action (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 effect(s) of the combination product. We are focused here on drug/device combinations.

Purports To Do

1. Simplify and expedite the review of combination products that qualify as devices - an instrument, apparatus, implement, machine, contrivance, implant…which is…intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or…intended to affect the structure or any function of the body of man or other animals, and which **does not achieve its primary intended** (continued on pg. 2)…

Success in Achieving Objective: +4

Unintended Consequences

1. FDA's Office of Combination Products assigns review to the appropriate agency center (drugs, devices, biologics), so, although sponsors provide a recommendation for which center should regulate the combination product, the FDA ultimately decides.
2. The statute gives the FDA full authority to use any and all agency resources in the review of the combination product – "nothing in this subsection shall (continued on pg. 2)…

Emergence of Unintended Consequences: –3

Potential Positive Impact on Innovation

1. When Congress revised the statute, it narrowed the exclusionary clause so that fewer products would be classified as drugs. The earlier version of § 321(h) provided that a product was a device if it did not "achieve any of its principal intended purposes through chemical action." [Medical Device Amendments of 1976, Pub. L. No. 94-295, § 3, 90 Stat. 539 (1976).] In contrast, the (continued on pg. 2)…

Positive Impact on Innovation: +3

Potential Negative Impact on Innovation

1. FDA discretion in applying the primary mode of action standard and in interpreting the definition of a device can essentially block the designation of many products, which, from a safety and efficacy perspective, could be adequately regulated under the device system.
2. Because of a lack of clear and useful standards on what causes a product to be excluded from (continued on pg. 2)…

Negative Impact on Innovation: –4

MI³ Score = 0

Recommendations

The combinations products policies are neutral for medical innovation. However, they could be very positive if the FDA honored the spirit of the law and the legislative history in:

1. making decisions on the primary mode of action of combination products,
2. applying the definition of a device, and
3. requiring companies to prove that there exist no potential or theoretical chemical actions. (continued on pg. 2)…

Purports To Do (continued from pg. 1)

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.

2. Reduce the number of combination products that would be considered drugs to include only those which rely on chemical action to achieve their primary intended purposes.

Potential Positive Impact on Innovation (continued from pg. 1)

FD&C Act now excludes from regulation as a device only those combination products that "achieve [their] primary intended purposes through chemical action." [Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16, 104 Stat. 4511 (1990).]

Unintended Consequences (continued from pg. 1)

prevent the Secretary from using any agency resources of the Food and Drug Administration necessary to ensure adequate review of the safety, effectiveness, or substantial equivalence of an article."

3. The FDA has overreached in the case of DSW (Diphoterine Skin Wash) by Prevor stating, "In determining whether an article is a 'device,' FDA must consider whether or not the article achieves its primary intended purposes through chemical action within or on the body of man. 21 U.S.C. § 321(h)...[I]f an article depends, **even in part**, on chemical action within or on the body to achieve any of its primary intended purposes, it does not meet the definition of a device." On remand from the Court, the FDA revised this position - FDA "interpreted the device exclusionary clause to mean that a product (or a constituent part of a combination product)...'does not achieve its primary intended purposes through chemical action' if the evidence indicates that chemical action does not **meaningfully contribute** to its primary intended purposes." However, the FDA cited no past precedent where "meaningfully contributes" substituted for "achieve" in the device definition.

Potential Negative Impact on Innovation (continued from pg. 1)

regulation as a device, many innovative products are not developed because FDA insists on a full scale drug review.

3. The combination product procedures necessitate that companies engage the FDA early in the development, well before companies have had enough time to ascertain whether their products have a significant chemical action. The agency insists on regulating combination products that do not have data on potential and theoretical contributions of the drug component to the mode of action as drugs, thereby defeating the purpose and intent of the regulations. The FDA routinely requires companies to prove the negative case in order to assign the review to the devices center, which is extremely difficult and often not feasible.

Recommendations (continued from pg. 1)

The FDA has full authority to call upon the resources of all centers in the review of combination products, therefore, its reticence to designate combination products that have some element of chemical action in achieving their primary intended purposes as devices is ill-founded. Although the reviews would be led by the device center, contributions from the drugs and biologics centers can be incorporated in the review and labeling of combination products designated as devices. Also, post-approval surveillance can address uncertainties. Until the agency honors the spirit of the law, combination products like the DSW skin washing system to prevent chemical burns will be stymied. Other combination products having adjunct materials that may exhibit chemical action but where the real intent of the product is to use physical modes of action to achieve the effect are also in (continued on pg. 3)...

Recommendations (continued from pg. 2)

significant jeopardy, for example, light activated wound healing and light activated dental cleaning products. Further limiting the device exclusionary clause by Congress could provide greater clarity, for example – "does not principally achieve its primary intended purposes through chemical action." However, even the word principally calls for judgment in applying the standard.

Since the device regulations are more suited for finely calibrating regulations based on product qualities, attributes, and risk, as opposed to drugs and biologics, which have a single framework, the FDA is missing the point, as well as an excellent opportunity to appropriately match review procedures with products. And, this hurts medical innovation. An excellent solution is contained in the Combination Product Regulatory Fairness Act of 2015, a bill recently introduced by Senator Johnny Isakson (R-Ga), and co-sponsored by Representatives Sens. Robert Casey (D-Pa) and Pat Roberts (R-Kan), which takes into account prior findings of safety and effectiveness of components of a combination product and assigns a leader center within FDA to address whether a product is reviewed as a drug, device, or biologic, based off of the primary intended purpose for the product. The legislation would allow sponsors to submit and work out an agreement with the FDA on a Combination Product Review Plan that details a clear regulatory process for the combination product, addressing necessary clinical studies, timelines, and an evaluation of incremental risks posed by the combination product.

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