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Cross-labeled combination products: A regulatory conundrum awaiting a solution

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When a device is intended for use with an already approved drug in a manner that is not consistent with the drug's approved labeling, regulatory challenges frequently emerge in determining whether the drug labeling must be changed to reflect its use with the device. This article highlights some of the unique regulatory considerations associated with cross-labeled combination products, particularly devices referencing drugs, in anticipation of an expected US Food and Drug Administration (FDA) guidance document this year.

Keywords – combination products, cross labeling, devices referencing drugs, drug delivery

Introduction

The Food and Drug Administration Modernization Act of 1997 (FDAMA) expanded the FDA's mission beyond the protection of public health to include the promotion of public health "by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner."[1] Since then, the agency has interpreted this mandate to include the fostering of medical product innovation. The agency has continually sought to facilitate innovation through the development of expedited review pathways, disease-focused centers of excellence, and new regulatory frameworks for novel technologies. However, there has been one category of combination products – devices intended for use with an already approved drug (devices referencing drugs, or DRDs) – for which the agency has not yet been able to provide a predictable and efficient review pathway. This article highlights some of the unique and challenging regulatory considerations associated with cross-labeled combination products, particularly those related to DRDs, in anticipation of a forthcoming FDA guidance document on cross labeling.

Regulatory background

A combination product is a combination of two of more different types of medical products, for example, a drug and a device, a device and a biological product, or a drug and a biological product. There are three ways by which the individual constituent parts of a combination product can be combined to meet the FDA's definition of a combination product:

- Physically or chemically combining the constituent parts as a single entity (e.g., a drug-coated device or a prefilled syringe);
- Co-packaging the constituent parts (e.g., a kit containing drugs and devices); or
- Cross labeling the separately provided constituent parts, where the constituent parts have "mutually conforming labeling."

The regulatory challenges presented by cross-labeled combination products emerge at least in part from ambiguities in the complex regulatory definition for cross-labeled products found in 21 CFR 3.2(e)(3):[2]

> A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.

In clarified terms, the drug and device collectively form a combination product:

- When a constituent part (e.g., a device in the DRD example) is intended for use only with an already approved, individually specified, different type of constituent part (e.g., a drug);
- When both the drug and device are required to achieve the intended effect; and
- If, upon approval, the labeling of the approved product (the drug in this example) must be changed to reflect its delivery by the device.

This applies even though the drug and device are neither physically/chemically combined nor co-packaged and are often sponsored by separate companies with no existing relationship.

To illustrate how the development of a DRD can go awry, based on the aforementioned regulatory framework, when a device company develops a new delivery system for an already approved drug, the DRD becomes a constituent part of a combination product if the FDA determines that the label of that drug

must be changed to reflect its delivery by the new device. Since combination products are assigned to a lead FDA center based on their primary mode of action (PMOA), and the PMOA ("most important therapeutic action") of a drug and its delivery device is nearly always attributable to the drug, the combination product would be assigned to FDA's Center for Drug Evaluation and Research for review. In this scenario, the device company finds itself in the unenviable position of having developed a device, likely with the expectation that the device would be eligible for a relatively smooth 510(k) review process, only to learn that approval or clearance of the device will be contingent on the concurrent approval of a drug labeling change. In addition to whatever approval or clearance may be needed for the device, approval of drug relabeling would likely need to be supported by adequate and well-controlled studies providing substantial evidence of the safety and effectiveness of the combination product. Similar issues arise when a new device is developed for "general" drug delivery when there is no drug approved for that route of administration (e.g., a device intended for delivery of drugs directly to a specific region of the body when there is no such drug currently approved). Such devices cannot be approved or cleared without the concurrent approval of a drug for such use.

The complexity for the device company is further compounded if the owner of the drug is not interested or willing to change its label to reflect drug delivery by that device. The drug company may be understandably concerned about both known and unknown risks associated with a different use of its drug than has been previously established. There may also be commercial concerns, which could arise, for example, if the device allowed more precise or localized delivery of the drug, resulting in less drug being needed to achieve the same, or potentially better, effect than when the drug is used as currently labeled. If the drug company is not interested in collaborating with the device company and if the device company is not interested or able (e.g., due to patent issues) to develop its own version of the drug, then there may be no practical means for the device company to pursue regulatory authorization of the device for that use. The agency lacks the authority to compel the two sponsors to cooperate, and the device sponsor cannot submit a supplemental new drug application (sNDA) to another party's application to change the drug label.

In contrast, in this same example, if the FDA instead determined that the label of the drug does not need to be changed, the device would have only "one-way" labeling referencing the drug. The device would be regulated by the agency's Center for Devices and Radiological Health (CDRH), largely avoiding the above challenges completely. Such use would be considered concurrent use of the two products rather than a combination product, analogous to general use delivery devices, such as unfilled syringes, infusion pumps, nebulizers, and catheters.

Addressing the DRD regulatory challenge

The FDA has periodically tried to work with the medical device and biopharmaceutical industries to develop a consistent and reliable regulatory

pathway for DRDs. The agency first addressed this issue by hosting a public workshop on Combination Products and Mutually Conforming Labeling in 2005. Indeed, in the Federal Register (FR) notice announcing the meeting and calling for public comments,[3] FDA stated:

> When the new product is intended to be used with the approved product in a way that is significantly different from ways described in the current labeling of the approved product (e.g., for a different indication, route of administration or dose), refusal by the sponsor of the approved product to submit a supplement may preclude mutually conforming labeling. In some cases, when the two sponsors do not work together, requiring that the two products have mutually conforming labeling could prevent the development of new products. FDA is concerned that valuable products may not be developed, manufactured, or distributed because of sponsor concerns about mutually conforming labeling.

Notably, the FDA Reauthorization Act of 2017[4] (FDARA) made significant progress addressing this issue with respect to a narrow segment of DRDs, medical imaging devices. The imaging device industry had long been frustrated by its inability to make available device settings, features or applications relying on the use of a contrast agent if the contrast agent had not been approved for such purpose. FDARA added Section 520(p) to the Food, Drug and Cosmetic Act (FD&C Act), which allows the FDA to approve or clear, through a device marketing application (premarket approval, 510(k), or de novo request), imaging devices that involve the use of a contrast agent, even if the contrast agent would be used in a:

- Concentration, rate of administration, or route of administration;
- Region, organ, or system of the body; or
- Patient population that is different from that described in the approved labeling of the contrast agent, as long as the differences from the labeling of the contrast agent do not adversely affect the safety or effectiveness of the contrast agent when used with the device.

The statute specifies that CDRH will have primary jurisdiction and the marketing application "shall only be subject to the requirements... applicable to devices." FDARA also added related Section 505(y) of the FD&C Act to permit the sponsor of a contrast agent to submit a supplement for such new use following approval of the corresponding device change under Section 520(p). However, such submission is not required.

Shortly after the promulgation of FDARA, the agency revisited the topic in 2017 with the publication of another FR notice[5] that discussed the agency's intention to use the premarket approval pathway for DRDs, instead of requiring drug relabeling through the NDA or sNDA pathways. The agency proposed that DRD sponsors would be eligible to use the PMA pathway if they were able to:

- Demonstrate safety and efficacy of the new use of the drug;
- Address the potential for user confusion or error that might otherwise occur due to inconsistencies between the drug and device labeling through the provision of adequate directions for the new use of the drug in the device labeling;
- Demonstrate that the likelihood for postapproval changes to the use of the marketed drug is low and that any changes that do occur are unlikely to raise safety or efficacy issues;
- Present a postmarket safety plan that will adequately address adverse events and medication errors related to the drug when used with the new device; and
- Provide all information needed to evaluate the safety and effectiveness of the new use of the drug in the device application, without relying on the drug company's proprietary information.

This approach shares similarities to that authorized under Section 520(p) of the FD&C Act for imaging devices and contrast agents, which provides a pathway for an imaging device to obtain approval or clearance for new uses of contrast agents if safety and effectiveness is demonstrated in the device application. Although the device industry supported the FDA's proposal in the 2017 FR notice,[6] it was opposed by the biopharmaceutical industry, which cited numerous legal and logistic challenges. In response to this feedback, the FDA withdrew its proposal in 2020.[7]

Issues requiring resolution

In November 2022, the FDA's Office of Combination Products (OCP) announced its intention to revisit this thorny issue with the issuance of new guidance in 2023.[8] In anticipation of the release of this new guidance, some of the key issues FDA must address to help resolve these regulatory issues are discussed here.

Articulating when mutually conforming labeling is required

Although the definition of a cross-labeled combination product has been in the regulations since 1991, the FDA has not yet elucidated the key underlying regulatory criterion, that is, when the labeling of the approved product must be changed. The codified text[2] cites several possible reasons the labeling may need to be changed ("e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose"), but these may be arguably construed as only examples due to the "e.g." in the codified language. Furthermore, these sections of the labeling are neither described as requirements (dictating a labeling change must be made when such sections are affected) nor are they identified as the only relevant labeling sections to be considered.

The FDA has encountered numerous situations over the years in which inconsistencies or contradictions in other portions of drug and device labeling might warrant changing the drug label. For example, some drug labeling describes the specialized training or experience of target healthcare providers, but the device might have been intentionally developed to broaden the user profile through a simpler method for the drug's delivery. It is not clear whether such a training statement would require an update to allow approval or clearance of the device. As another example, a systemically administered chemotherapy drug might be indicated for a particular tumor location, but a device might allow the drug to achieve greater concentrations at that location, even if the drug is otherwise administered in a manner that is entirely consistent with its labeling. It is not clear what sections of the drug label must be evaluated to determine whether revisions are needed, what degree of contradiction or inconsistency (if any) is permitted without changing the labeling, or when such contradictions or inconsistencies are never acceptable.

Another area requiring clarification is the meaning and interpretation of "individually specified" in the codified definition of a cross-labeled combination product.[2] Often, "individually specified" in the context of a DRD has been taken to mean the identification of one particular drug product, but it is not clear whether such drug would be "individually specified" by brand name or generic name (the latter of which could be construed to be both a brand name drug and its generic equivalents). It is also possible that "individually specified" could be more narrowly construed to mean a particular dosage form or strength of a particular drug product. This is another area for which clarity in the forthcoming guidance would be helpful.

Although the FDA approaches product labeling with significant rigor in most other respects, the lack of clear principles to determine when the labeling of an approved product must be changed to reflects its concurrent use with another product has at times led to uncertainty in the regulatory process; ad hoc, case-by-case, and/or subjective regulatory decision making; and inconsistent outcomes. All these factors, combined with the potential inability to bring to market a safe and effective device if cross labeling is needed, can stifle product innovation, arguably in conflict with the agency's mandate under FDAMA. By defining clear principles articulating when the labeling of an approved product must be changed, the OCP's forthcoming guidance would go a long way in improving the understanding by agency staff and sponsors of this complex regulatory situation and help foster innovation for novel DRDs. It is recommended that the guidance clarify which sections of the labeling should conform between the two products, to what extent (e.g., must the labeling be identical, consistent, or simply not contradictory), and whether conformity is more important for some parts of the labeling than for others. Notably, these are the same goals the agency sought to address in the 2005 public workshop, as described in the FR notice for the meeting.[3]

Sponsor cooperation

Another challenge the agency faces in promoting innovation is its inability to compel two entities to cooperate. Should a drug applicant not be willing to work with the manufacturer of the new device, the FDA's toolbox to incentivize cooperation is severely limited and would likely require new legislation, for example, with respect to user fees, exclusivity, or other measures. Moreover, as some sponsors noted in response to the agency's 2017 proposal,[9] the likelihood of a manufacturer securing a marketing authorization for a DRD without the cooperation of the drug sponsor is low owing to the extent of data needed to support an application. Specifically, a DRD sponsor would likely need to include information on drug formulation, specifications, performance, and drug-device interactions, which may be proprietary to the drug sponsor. This requirement appears to make the FDA's suggestion to reference publicly available data infeasible, as most of these data would not be in the public domain. Nevertheless, in the interests of public health and fostering product innovation, it is worth exploring potential regulatory pathways for DRDs in the absence of cooperation, especially when a new DRD has the potential to significantly improve safety or effectiveness. Potential regulatory or statutory changes, perhaps like those promulgated in Section 520(p) of the FD&C Act for imaging devices, should also be considered.

Legal issues

Device sponsors seeking to ease patient burden or improve the safety, efficacy, or convenience of use of a previously approved drug are often stymied by their inability to reference the drug's data. Absent the consent of the drug sponsor, any attempt by the device manufacturer to reference the data may infringe upon the drug sponsor's Fifth Amendment rights to private property. Commenters noted in 2017 that the FDA's attempt to address this issue by encouraging sponsors to reference publicly available data was not only infeasible, but also likely fell afoul of these Fifth Amendment concerns.[10]

Underscoring the challenge that private property rights pose to cross labeling, the Oncology Center of Excellence addressed this issue in its guidance on cross labeling oncology drugs in combination regimens,[11] by restricting a sponsor's ability to cross label only to drugs to which it has rights. The guidance states that cross labeling for oncology drug combination regimens is permissible only for "oncology drugs for which the applicant owns or has a right of reference to the data demonstrating the safety and effectiveness of the new combination regimen for an oncological disease."

Another legal issue concerns the possibility that the DRD label may misbrand the drug if the device's novel use of the drug is referenced only in the device label. A drug or device is considered misbranded unless its labeling bears adequate directions for each intended use. It is not clear whether third-party labeling of a DRD creates a new intended use for the drug that would require an

otherwise non-cooperating drug company to update its labeling so that the drug is not misbranded.

Evidentiary standards

Section 505(d) of the FD&C Act requires demonstration of the safety and "substantial evidence of effectiveness" of drugs through the NDA or sNDA pathway. However, the FDA's 2017 FR notice proposed that, as an alternative to DRDs being regulated as a drug, they could be regulated as a device under the PMA pathway. The FDA has historically equated the regulatory approval standards under the NDA and PMA pathways – and Congress went further in FDARA for imaging devices and contrast agents by also permitting the use of the 510(k) process, which requires demonstration of "substantial equivalence." However, some stakeholders have expressed concern that the statutory approval standard for PMAs is arguably lower than that for NDAs – requiring sponsors to provide "reasonable assurance" rather than "substantial evidence" of safety and effectiveness. To the extent the forthcoming guidance relies on the use of the PMA approval process, it would be helpful if the guidance explained FDA's interpretation of these review standards.

Postmarket challenges

Cross-labeled combination products also pose a variety of postmarket challenges, especially when the drug and device sponsors are not collaborating. A DRD's safety and effectiveness would likely have been fully established with the formulation of the drug available at the time of supporting studies, but there is concern that the drug formulation could change over time in a manner that may affect its future compatibility with the device. If the drug and device companies are collaborating, presumably information about an upcoming change would be communicated between the parties and appropriately evaluated to confirm any impact on safety or effectiveness. When there is no such relationship, however, the device company may have no means to become aware of such a change until after the change to the drug is approved, and even then, it is possible that publicly available information (e.g., through the FDA's approval database) may not include sufficient information for the device company to evaluate the impact of the change. The agency has previously proposed that the device company in such a scenario could be required to monitor approvals for changes to the drug as a condition of PMA approval, as well as to test the drug supply on an ongoing basis to ensure continued safety, effectiveness, and compatibility with the device, but even those requirements could fail to identify all such changes made by the non-cooperating party.

From a postmarketing reporting perspective, 21 CFR 4.103[12] includes the requirement for sponsors to share postmarket safety events with the applicant of the other cross-labeled constituent part (i.e., the "constituent part applicant" as defined in the regulation). For example, when one constituent part applicant receives information regarding an event that involves a death, serious injury, or

adverse experience, they must provide information about the event to the other constituent part applicant no later than five calendar days of receipt of the information. Perhaps an analogous requirement could be considered for communicating postmarket changes for cross-labeled combination products as well for such changes between otherwise non-cooperating product sponsors with one-way labeling.

Conclusion

While there are numerous challenges presented by cross-labeled combination products, including DRDs, the FDA has a long history of demonstrated flexibility and an openness to partner with industry to develop innovative approaches to address similar issues. To advance medical product innovation and patient access, the FDA needs to make meaningful progress in resolving the longstanding cross-labeling conundrum in its forthcoming guidance. The agency must explore whether regulatory changes (e.g., in the definition of a cross-labeled combination product) are warranted. Given the regulatory, legal, and competitive challenges involved, Congressional action such as that taken under Section 520(p) of the FD&C Act for imaging devices and contrast agents may ultimately be required to fully address this issue and protect the agency from potential legal challenges by some stakeholders who may feel disadvantaged by whatever changes are made.

Abbreviations

510(k), premarket notification submitted under Section 510(k) of Act; **FD&C,** Food, Drug and Cosmetic [Act]; **DRD,** devices referencing drugs; **FDARA,** FDA Reauthorization Act; **FDAMA,** Food and Drug Modernization Act; **FR,** Federal Register; **NDA,** new drug application; **PMOA,** primary mode of action; **sNDA,** supplemental new drug application.

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