



January 29, 2010

VIA ELECTRONIC SUBMISSION

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Postmarketing Safety Reporting for Combination Products; Proposed Rule; Docket No. FDA-2008-N-0424

Dear Sir or Madam:

The Combination Products Coalition (“CPC”) is pleased to offer its comments on the Proposed Rule for Postmarketing Safety Reporting for Combination Products.¹ This proposed rule is a critical first step in providing clarification on postmarket safety reporting requirements for combination products. The rule clearly is the product of a tremendous amount of time and effort, and we thank the Agency for its thoughtful analysis.

By way of background, the CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in the combination products area. One of the principal goals of our organization is to work with the Agency on issues affecting combination products, in order to advance our common missions of providing the best possible health care for patients. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

Below we offer our comments on the proposed rule. We have general, overarching comments on the proposed rule as well as several specific comments. Ultimately, although the framework set forth in the proposed rule is expected and understandable, we hope that the rule serves as a bridge to a unified regulatory system, rather than a system comprised of existing, divergent requirements. Our specific comments focus on aspects of the rule that need to be clarified to ensure regulated industry and FDA personnel can implement the new requirements appropriately and in a timely manner.

¹ 74 Fed. Reg. 50744 (Oct. 1, 2009).

GENERAL COMMENTS

The proposed rule is an important development in combination products regulation. Its issuance will facilitate public dialogue on postmarket safety reporting requirements and will help regulated industry structure reporting systems for combination products. Because of this significance, the rules need to be implemented in a deliberate, thoughtful manner.

1. The rule should be part of the bridge to unified regulation

We believe that the framework described in the proposed rule – and any similar framework that attempts to combine the different drug, device, and biological product regulations – should be considered an *interim* solution until a unified combination product regulatory framework is developed and ultimately, until a unified regulatory framework is developed for all FDA-regulated medical products. In terms of postmarket safety reporting requirements, a unified reporting process would mean there would be just one type of report that asks for all relevant information for a regulated article, whether it is comprised of a device, biological or drug or a stand-alone article. There would also be one integrated set of time periods for reporting.

The benefits of such approach seem significant both for the Agency and for industry. A detailed discussion of these benefits and other aspects regarding the implementation of a unified system may be found in the comments the CPC filed in response to the Agency's adverse event concept paper. These comments are available at: <http://combinationproducts.com/images/CPCAEConceptPaperFiled3.23.06.pdf> (see in particular pages 6-8).

2. Impact of the proposed rule

The proposed rule will have a far-reaching impact on combination products that are under development and currently marketed. A significant number of products already fit the definition of a combination product, and these numbers are only expected to increase. To quantify this statement a bit, in 2005, the combination products market was estimated at \$6.4 billion and expected to reach \$11.4 billion by 2010.² Some sources estimate that 30% of new products under development are combination products.

FDA has acknowledged that these increases in the discovery, research, and marketing of combination products has and will continue to substantially impact the types and numbers of products falling under the FDA's regulatory authority. For example: "FDA expects to receive large numbers of combination products for review as technological advances continue

² BCC Research, Drug-Device Combinations (June 2005) (obtained from MaRS Venture Group, Emerging Technology Brief (Sept. 2006)).

to merge product types and blur the historical lines of separation between FDA’s medical product centers”³

FDA data already evidence the increasing numbers of combination products. For example, the most recently published performance report from FDA’s Office of Combination Products (OCP) shows that three key combination product-related activities (products submitted for review, intercenter consultation requests, and assignment requests) have steadily climbed, reaching their highest point since OCP’s inception in 2002.⁴

In all, the numbers of combination products being developed and marketed can only be expected to increase. As a result, neither industry nor the Agency should underestimate its importance and the likely impact on the Agency or regulated industry. Specific issues related to implementation and potential impact of the new rules are discussed below.

SPECIFIC COMMENTS

In addition to the above comments, we have a number of specific comments on the substance of the proposed rule.

1. Reporting events to manufacturer of constituent part or to FDA

Although the bulk of the proposed rule represents a synthesis of existing requirements, proposed § 4.104 is the one area that is completely new. We presume that for the existing requirements, the proposed rule does not change the information required to be reported, reporting forms, and similar requirements. However, the Agency needs to specify the “who, what, when, where, and how” for the new requirements in § 4.104. As currently written and described, these new requirements are essentially incomplete and will be difficult for the Agency and industry to operationalize. Below we identify a number of specific logistical issues that warrant clarification.

a. Information required to be reported

This provision needs to be clearer on *when* information needs to be reported, and on *what* information the reporter is required to submit to the other applicant or to FDA. The proposed regulation simply references reporting “information” the reporter received about the event. The use of the word “information” without further description or explanation is ambiguous.

Proposed Solution: In terms of when and whether information must be reported, the rule should clarify that reporting under proposed § 4.104 is required only if the reporter has determined a *potentially reportable event* exists under proposed § 4.103(a). The Agency has proposed a similar standard in the past for drug reporting

³ FDA, About Combination Products, *available at:*

<http://www.fda.gov/CombinationProducts/AboutCombinationProducts/default.htm> (last accessed Dec. 14, 2009).

⁴ FDA, OCP FY 2007 Annual Report.

requirements – i.e., that reporting is required for events where there’s a reasonable probability of causation with respect to the product in question.⁵ We think this is the correct standard. Similarly, the rule should clarify that if an applicant can reasonably determine that an event does *not* concern another applicant’s constituent part, the event does not need to be reported to the other applicant or to the Agency.

The implementing guidance should also provide suggestions on what information is required to be reported.

Proposed Solution: The implementing guidance should provide examples and suggestions of information that should be shared with the other manufacturer or FDA when there is a potentially reportable event. For example, in some cases, the reporter may need to report all available information on the event, including the information that the reporter used to determine that the event was potentially reportable.

b. *Reporting to FDA “or” another applicant*

By its plain language, the rule provides that the reporter submitting the information is free to choose whether the information is submitted to the other applicant *or* to FDA. The rule should clarify when reporting information to FDA is appropriate.

Proposed Solution: If a company receives information not exclusively related to the products for which it holds a marketing application(s), that company should report to other manufacturers and/or marketing application holders, to the extent that such reporting is practical and the reporting manufacturer does not have other reasonable concerns about providing the information to another manufacturer (e.g., revealing proprietary or confidential information). If such reporting is not practical or the manufacturer has concerns about providing the information to another manufacturer, then the company must report to FDA.

c. *Reporting obligations of nonapplicants*

The way in which this new proposed requirement is written raises the possibility that a constituent part manufacturer that doesn’t hold a marketing application may need to file adverse event reports with FDA. This result is inappropriate and would greatly upset existing established frameworks. The final rule and implementing guidance should clarify that this is not the rule’s intent.

We think this confusion arises because, as discussed in more detail under our second specific comment (page 7), there is ambiguity on the inclusion of component parts in the definition of constituent part. This ambiguity makes things really confusing when one considers language in the preamble that’s intended to explain the new requirement. In particular:

⁵ 68 Fed. Reg. 12406, *Proposed Rule: Safety Reporting Requirements for Human Drug and Biological Products* (Mar. 14, 2003).

If you do not hold all of the applications used to approve or clear the constituent parts of your combination product, you would comply with the requirements for postmarketing safety reporting associated with the application used to approve or clear your constituent part of the combination product. Additionally, under proposed Sec. 4.104(a), you would submit the information you receive about an adverse event to FDA or the reporter for the other constituent part of the combination product within 5 calendar days of your receipt of the information. Under proposed Sec. 4.104(b), if the other reporter receives such information from you, that reporter⁶ would then investigate and report the event in accordance with the statutory provisions and regulatory requirements for postmarketing safety reporting for their constituent part of the combination product.

This reading implicates the following scenario: Person A must report information to a non-application holder (Person B). Upon receipt of the information, § 4.104(b) requires Person B (who doesn't hold an application) to investigate and possibly report the event relating to their product. Further, because of the confusion on the definition of constituent part, Person B could be a mere component part manufacturer.

For a more specific example, consider a prefilled syringe approved under an NDA where no 510(k) exists for the syringe part. The manufacturer of the syringe sells the syringe as unassembled components to the NDA holder, and also sells the syringe components to other device and drug manufacturers. Under proposed § 4.104(b), the syringe manufacturer would have to investigate information received from the NDA holder(s) and report any events in accordance with proposed § 4.103(a) and (b). Thus, as drafted, it seems the proposed rule could require component manufacturers to report adverse events.

The results described above – requiring reporting for entities that do not hold a marketing application -- are not appropriate. Marketing application holders are in the optimum position to understand a potential reportable event and meet reporting obligations. The application holder knows the product, labeling, actual use, and potential impact on the patient. In the example described above, the device component manufacturer simply cannot do as good of a job investigating the event as the marketing application holder. Requiring reporting from nonapplicants also would unnecessarily conflict with existing established frameworks. In all, requiring the reporting of information from another manufacturer should be managed from the finished product perspective – indeed, many manufacturer/supplier relationships entail agreements that incorporate requirements to fulfill this objective.

⁶ Under the proposed rules, the term “reporter” (and any reference to “you”), includes anyone responsible for evaluating and determining whether an event meets the criteria for postmarketing safety reporting – it’s not limited to an applicant.

Proposed Solution:

Below we offer a solution for addressing the definition of a constituent part.

In addition, the final rule and implementing guidance should provide a clear explanation of the intent of § 4.104(b), clarifying that the intended result is that if the person responsible for the combination product (we'll call them person "A") receives information from either another person who holds an application used to approve or clear a constituent part of the combination product, or a person who legally markets the constituent part of the combination product without an approved or cleared marketing application, person "A" must investigate and report the event.

Finally, the final rule and implementing guidance should clarify that only marketing application holders are required to file adverse event reports with the Agency under these rules. Reports relating to a constituent part that does not have a marketing application would be handled under the postmarket safety reporting rules that apply to the combination product's marketing application, plus the "supplemental" reports required under § 4.103.

d. Five-day reporting timeframe

We're also concerned that the five-day reporting timeframe for this new requirement is not a reasonable approach for all reports. In particular, events often simply cannot be investigated within such a short timeframe. Further, in some instances, a party may not have an established relationship or reporting pathway with another party. In these cases, it may well take longer than five days to find the right person at the other company.

We recognize that in some instances, under drug regulations, five-day reports between manufacturers are required.⁷ However, these requirements illustrate the principle that a five-day timeframe is appropriate to facilitate reports that have a shorter timeframe, and by entities that have an established tie to the product. In particular, the drug regulations' five-day reporting timeframe between manufacturers pertains to drug "alert reports" concerning adverse drug experiences that are both serious and unexpected. Nonapplicants whose names appear on the label of the drug as a manufacturer, packer, or distributor must submit those alert reports to the Agency within the standard 15-day timeframe. However, these nonapplicants can elect to submit the report to the applicant instead. If the nonapplicant elects this option, the nonapplicant must submit the report to the applicant within five calendar days of receipt of the report by the nonapplicant. Thus, this five-day timeframe is only for events (1) that could pose a high risk to the public health; and (2) that are coming from entities that have an established tie to the product. A five-day timeframe should not be used as a one-size-fits-all approach for all adverse events.

Proposed Solution: Tie the reporting timeframe to the identified event -- reports that would otherwise be required to be reported within five days or less would have an expedited timeframe; other reports could have a longer timeframe.

⁷ 21 CFR 314.80(c)(1)(iii).

e. Implementation

The proposed rule states that reports under this new requirement will be submitted using existing methods identified in the underlying regulations. However, the proposed rule does not identify any mechanism for submitting reports under proposed § 4.104, even though these are new requirements. We are also not aware of any tracking mechanism within the Agency that will enable it to assess interactions between reporters under proposed § 4.104.

Proposed Solution: In terms of reporting potential events and related information to other applicants, reporters should be permitted to choose their usual or other internally-developed format for reporting. The final rule and implementing guidance also need to identify the format for reports to the Agency and explain how the Agency will track and assess compliance with this new requirement.

2. Constituent parts

a. Definition

As written, the definition of a constituent part seems to encompass any device or drug component or ingredient. Specifically, the proposed rule defines a constituent part to include a drug, device, or biological product that is part of a combination product.⁸ As we know, the statutory definitions of a device and a drug include components and ingredients.⁹ As a result, the current definition of constituent part in effect reaches backward to component and ingredient manufacturers, making their products regulated as though they were finished devices or drugs.

Proposed Solution: The final rule should set forth a definition of “constituent part.” This definition needs to make clear that components and ingredients are not subject to these rules and that a constituent part consists of a finished device or drug product or substance. In particular, we suggest the definitions in proposed § 4.101 are revised as follows:

“Constituent part is a drug, device, or biological product that is part of a combination product as defined in § 3.2(e) of this chapter and that contains a drug substance as defined in § 314.3

⁸ Proposed § 4.101. We also note that this definition says “is part of a combination product as defined in § 3.1(e) of this chapter.” The reference to § 3.1(e) appears to be a mistake and probably should be a reference to § 3.2(e).

⁹ The term “device” ... means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory (21 USC 321(h) (Emphasis added). The term “drug” means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (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 in clause (A), (B), or (C)* (Emphasis added). 21 U.S.C. § 321(g) and (h).

of this chapter or that is a finished device as defined in § 820.3 of this chapter, or a biological product as defined in § 600.3 of this chapter.”

Add the following definition: “Component means any raw material, substance, piece, part, software, firmware, labeling, assembly or inactive ingredient that is intended for use in the manufacture, or to be included as part of the finished, packaged, and labeled combination product.”

b. Assessing causation

The proposed rule recognizes that reporters often may need to assess which constituent part is associated with a particular adverse event. Assessing causation obviously has a critical impact on what reporting requirements are triggered. For example, if it’s unclear which constituent part led to an event, the reporter must satisfy reporting requirements for each constituent part. However, the rule does not provide any detail or direction on assessing the relationships between adverse events and constituent parts.

Proposed Solution: The implementing guidance needs to offer suggestions on the investigational steps an applicant should take in determining whether a constituent part “reasonably” caused the adverse event.

3. Submitting reports on combination products involving multiple applications

The proposed rule addresses situations in which multiple marketing applications exist for the individual constituent parts of a combination product. On one hand, the rule explains that when there are two marketing applications for a combination product, and a reporter can reasonably determine the constituent part that caused the adverse event, the reporter may consider only that constituent part in determining reporting requirements. However, if it is unclear which constituent part led to the adverse event, the reporter must satisfy reporting requirements for each constituent part of the combination product. In this way, the rule is ambiguous on what reports need filed and by whom when an adverse event relates to the “combination product” (i.e., when the event is a result of more than one constituent part), as opposed to a single constituent part.

Proposed Solution: The rule should more clearly define what reports must be filed for the various constituent parts when multiple marketing applications exist. In particular, if a company can reasonably determine that an adverse event is *not* associated with a particular constituent part, that company does not need to file a report with the Agency. When the adverse event relates to the combination product as a whole, as opposed to an individual constituent part, the application holder(s) for the combination product should file the report.

4. Reconciling supplemental/overlapping reporting requirements

As the rule recognizes, there are some important differences among reporting criteria for differently regulated articles that will necessitate certain supplemental and possibly duplicate reports. In this regard, the proposed rule should clarify and provide more examples of instances in which duplicate reports are necessary. For example, it seems that for a combination product with two constituent parts and two marketing applications, we can think of up to five reports that could be filed for just one adverse event.

- Report under marketing application for constituent part one (e.g., drug)
- If ambiguous, another report for constituent part two (e.g., device)
- Report to other application holder (e.g., device holder)
- Report by other application holder
- Report to FDA

Obviously, this type of scenario becomes even more complicated for combination products with more than two constituent parts and marketing applications. Providing examples of complex situations like these will help applicants understand and implement requirements appropriately.

Further, in discussing the supplemental requirements in proposed § 4.103(b), the rule explains that the supplemental reports are only necessary if the reporter “would not otherwise (already) be required to provide them under the reporting framework associated with the application under which your product is approved, or if they would be required, but at a later timeframe.”

Proposed Solution: The final rule and implementing guidance needs to explain when supplemental reports are required for instances in which reports are required, but at a later time. By definition, the reports in proposed § 4.103(b) are *supplemental* reports that capture events not otherwise captured under a product’s primary reporting scheme. The final rule should clarify that this language regarding capturing reports at a later time is intended to capture situations in which multiple constituent parts are involved in an event.

5. Reporting to the lead Center

The proposed rule specifies that for combination products approved under one marketing application, applicants will report all adverse events to the lead Center. However,

the proposed rule does not seem to address instances in which there are multiple marketing applications.

Proposed Solution: The final rule should clarify that the combination product marketer will report to the lead Center, while those holding applications for constituent parts (which may or may not be the same entity holding the combination product applicant) will continue to report to their individual Centers. In cases where there is only one marketing application for the combination product, and the lead Center requests a marketing application be filed for a constituent part, the holder of that additional marketing application should file reports with the Center under which the marketing application is cleared or approved.

The Agency also should also ensure that the lead Center has the necessary expertise to review adverse events for all constituent parts. This may include training, issuance of guidance, and cross-assignment of personnel. We discuss this issue in more detail below.

6. Implementation issues

a. Need for implementation phase

A significant issue with regard to implementing the proposed rule is how the rule will be implemented for existing, legacy combination products. As discussed above under our general comments, the proposed rule will have a far-reaching impact on products under development and currently on the market.

Combination products already on the market may have reporting frameworks established through product approvals and commercial agreements, and they typically will have established technological reporting mechanisms. The proposed rule presents complex technological issues in terms of the gateways and information flow for both company and Agency adverse event systems. Consider the simple example of a combination product approved under an NDA. Currently, the only way to input information relating to a device constituent part would be through the NDA gateway.

Complicating internal company issues will be the Centers' implementation of the new rules. Agency personnel will need to handle certain types of reports with which they may be unfamiliar, which may present IT and personnel challenges. We suspect that the rule's implementation may entail a significant amount of intra-agency training and even re-engineering of IT systems. Also, as described above, currently there seems to be no mechanism to handle the new reporting requirements in proposed § 4.104.

The proposed rule underestimates the practical challenges involved in implementing this new reporting framework. For example, the proposed rule estimates that "there are no significant operating and maintenance costs associated with this collection of information because ... reporters are required to develop and maintain systems for reporting and

maintaining records of postmarketing safety events.” Because these systems are already in place, “reporters will accrue no significant additional costs” Further, the rule estimates the time associated with preparing reports as minimal – only one hour to prepare and submit a report and only a half hour to fulfill corresponding record-keeping requirements.

In addition to the significant challenges for *existing* combination product manufacturers, the above estimates do not seem to have considered that the proposed framework may be new and quite unfamiliar to many manufacturers. Until now, the Agency has expressed its interpretation of post-market safety reporting for combination products through a concept paper. Although many firms experienced in combination product issues have taken comprehensive and conservative approaches toward post-market safety reporting, other firms that are new to the combination product area may not have incorporated such practices. Ultimately, the process and analysis required to implement new rules like these within a company requires the coordination of many functions and extensive communications and analysis among company personnel. It may also entail time- and labor-intensive changes to heavily automated reporting systems.

Proposed Solution: The estimated burden on manufacturers should be increased significantly, and the Agency should re-evaluate the implementation deadline. In all, 180 days may not be sufficient for delaying the rule’s effective date, particularly for existing products where existing reporting systems may have to be revamped. We recommend the Agency give manufacturers a year to implement the new requirements.

b. *Developing new guidance and using existing guidance*

The proposed rule is complex in its application to a wide variety of products and application holders and its synthesis of multiple regulatory frameworks. Coordinating guidance on this rule and other existing postmarket reporting regulations is essential to ensure smooth implementation of the final rule. In particular, outlining the requirements in a table or matrix format would be tremendously helpful. Existing safety reporting guidance may also serve as guidance on how to implement the new rules for combination products. Guidance to the field force also is a critical component of the implementation phase.

Proposed Solution: The Agency should issue specific implementing guidance *before* the final rule is published in order to enable public input that also might be useful for developing the final rule. The Agency should then issue a final guidance in tandem with the final rule. In addition to clarification of the issues identified above, this guidance should have flowcharts and should map the various requirements in a table format, in order to assist manufacturers in determining what reports are necessary under the new rules. The implementing guidance should address how companies should apply existing guidance for safety reporting (e.g., MDR guidance).

The implementing guidance and field force guidance should address how Agency personnel will coordinate to ensure compliance and how the Agency will monitor these new requirements.

c. Cross-labeled combination products versus concomitant use

FDA needs to distinguish between cross-labeled products as defined in 21 CFR § 3.2(e)(3) and concomitant use in order to clarify the application of these rules. Previously, the Agency has explained that concomitant use of two differently regulated products is not a combination product.¹⁰

Proposed Solution: The Agency should re-affirm this fundamental principle in the context of these rules to ensure understanding, particularly by new market entrants that may not be as familiar with the history of combination product regulation.

d. Issues specific to medical devices

The proposed rule also raises a number of issues specific to medical devices. First, in describing reports for device malfunctions, the proposed rule references and relies upon new provisions enacted under section 227 of the Food and Drug Administration Amendments Act of 2007 (“FDAAA”). These new requirements would allow summary reporting for malfunctions relating to class I devices, while standard 30-day malfunction reports would be required for only certain devices, such as class III devices and class II devices that are permanently implantable, life supporting, or life sustaining. The proposed rule makes it sound like these requirements have been implemented, yet we understand that currently the Agency has not established a timeframe for the FDAAA requirements.

Proposed Solution: The rule should clarify this ambiguity and provide that summary requirements only go into effect when the FDAAA requirements do.

The rule or implementing guidance should also address how 21 CFR Part 806 (device corrections and removals) fits into the proposed post-market safety reporting scheme. In particular, in the device context, the Agency has explained that a correction or removal report is not required if the information has already been provided to FDA.¹¹

Proposed Solution: The final rule and/or implementing guidance should reaffirm that a correction or removal report is not required if the information has already been provided to FDA under these new rules.

e. Interaction with ex-U.S. reporting requirements

For regulated industry, an important component of implementation is the new rules’ interaction with ex-U.S. reporting requirements for U.S.-manufactured products, which also will increase the burden on manufacturers. In the past, the Agency has considered

¹⁰ 56 Fed. Reg. 58754, *Assignment of Agency Component for Review of Premarket Applications* (Nov. 21, 1991).

¹¹ See FDA, *Device Advice, Recalls, Corrections and Removals (Devices)*, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/RecallsCorrectionsAndRemovals/default.htm> (last accessed Dec. 2, 2009).

harmonization with global requirements for post-market safety reporting when proposing changes.¹²

Proposed Solution: The Agency should consider global harmonization issues in developing the final rule. The Agency also needs to clarify where manufacturers should submit field reports when the report is from a foreign manufacturing site.

* * *

We are pleased that the Agency has issued the proposed rules, and we look forward to the final rule, implementing guidance, and ultimately a unified combination product reporting scheme. Because of the important implications of these rules, we urge the Agency to carefully consider stakeholder comments as it develops the final rule. We are happy to help in any way we can.

Respectfully submitted,



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¹² *Id.*