American Medical Systems

10700 Bren Road West
Minnetonka, MN 55343 USA

Phone: 952-933-4666
Fax: 952-930-6157

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Food and Drug Administration
Dockets Management Branch HFA-305
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No. 02N-0445
Responses to Request for Comments

To Combination Products Program:

Thank-you for the opportunity to respond to questions regarding FDA policy initiatives regarding combination products. AMS is a midsize medical device manufacturer (500 employees) producing Class I, II, and III devices to treat incontinence, erectile dysfunction (ED), and urinary obstruction, primarily benign prostatic hyperplasia (BPH). Our current experience with combination products has been limited to the drug/device combination, therefore, our comments to each of the questions the FDA posed in its Federal Register Notice 02N-0445 pertain most directly to the drug/device combination component.

1. **What types of guiding scientific and policy principles should FDA use in its revisions to the existing Intercenter Agreements that allocate review responsibility for human medical products?**

Response:
As a starting point for regulatory activities concerning combination products, the Agency may consider separate guidelines for different combination product categories. For example, differences in technology, clinical trial designs, manufacturing environments and post-market surveillance for a drug/device product vs. a biologic/device product may prove too great for a single policy. Once the combination product has been classified as a drug/device, device/biologic, biologic/drug, etc. then it can be subjected to the guiding scientific and regulatory policy principles for that combination product class developed by the Agency. So, the first step is to classify the combination product using a consistent and public classification process.

The guidance on primary mode of action should be further defined. Historically, if the combination product uses an approved product and an unapproved product, the issue of new questions raised by the unapproved product must be considered. The Intercenter Agreement provides that if the primary mode of action relates to structure, physical, repair or reconstruction then CDRH takes the lead. For example, if the primary mode of

action is chemical such as a chemo-ablative agent which performs a structural or repair function, then the chemo-ablative agent should be considered a device. However if it cannot be determined from prior information that the ablative effect is limited to structure but has systemic effects also, then CDER would lead.

Separate review of the scientific issues raised by the drug and device components should be done. Specifically, a risk/benefit analysis for each will point the direction for further review. If the risks to the patient are greater or are undetermined because of the use of one of the components, then the center for that component should conduct a review but not necessarily be the lead reviewer. The agency should consider the opportunity for a true "co-review" or team review rather than limit the process to a primary review center.

In regard to FDA policy, the Combination Product Program has a number of new initiatives that have been proposed.

1) Developing standard operating procedures for the review of combination products will be very helpful. This should include a guidance on the Request for Designation (RFD) process.
2) As mentioned above, the Intercenter Agreement should be revised to include more complete definitions based upon examples from the history of decisions made since the Agreement was initiated. In addition, there are 3 Intercenter Agreements. The three documents should be combined into one document or at minimum reworked to be parallel documents.
3) Communicating recent jurisdictional decisions to the regulated community will be an important component.

2. **What factors should FDA consider in determining the primary mode of action of combinations? In instances where the primary mode of action of the combination product cannot be determined with certainty, what other factors should the agency consider in assigning primary jurisdiction? Is there a hierarchy among these additional factors that should be considered in order to ensure adequate review and regulation (e.g., which component presents greater safety questions)?**

Response:
Presently, SMDA requires combination product jurisdiction decisions to be based on the product's primary mode of action. However, the statute and regulations fail to define primary mode of action.

Drug/device combination products have more than one component and each component may have a different principle of operation, operating mechanism, or mode of action. By definition, the combination product is a "single entity" and therefore must have a primary mode of action, although it may be difficult to discern. The indication for use can be an important factor in discerning the primary mode of action.

The indication for use typically is related to the primary mode of action and may offer insight in cases where the primary mode of action initially appears uncertain. For example, a drug-coated catheter can be used to open an occluded artery (heparin-coated angioplasty catheter) or deliver a dose of drugs through an open artery (drug delivery

catheter). Both products use essentially the same device component and a drug component. In the first case the device has primacy and in the second case the drug has primacy. Once the indication for use is considered, the primary mode of action becomes more clear. In drug/device combinations, the primary mode of action is closely associated to the existing definitions for drugs and devices. As a possible heuristic for these combination products, look to the indication for use as the arbiter in cases where the primary mode of actions appears uncertain and/or press the Sponsor to declare a primary mode and indicated use for the combination product.

The primary mode of action always should be determinable by the Agency. If the agency cannot determine the primary mode of action with certainty, either the Agency has not been supplied with all facts (or they are poorly presented by the Sponsor) or the Sponsor has not completed its own research on the product and failed to declare a primary mode of action.

Combinations products used by physicians to treat or diagnose similar conditions among similar patient populations should be assigned consistently to the same Center and that Center should be responsible for both the premarket review and postmarket regulatory activities. In accordance with the spirit of the Least Burdensome principles, redundant regulatory filings by industry and review by the Agency are squander resources and promote inefficiencies. For example, consistent assignments of a combination product to CDRH and subsequent postmarket surveillance reporting into the MAUDE system and eliminate any need to collect data from other postmarket surveillance systems maintained by the Agency. The result is more accurate and complete data set that promotes efficiencies and---when required---responsiveness from the Agency.

Risk-based criteria are appropriate for *product classifications* but **not** for primary jurisdictional decisions regarding combination products. Identifying the component with the highest level of risk and assigning the corresponding center as the lead defies the current regulation and dismisses other salient criteria for marketing application review (clinical trial design, effectiveness, technology). All three Centers and current marketing applications are capable of obtaining and reviewing the data necessary for safe and effective products.

3. **What are the general scientific and policy principles that should be followed in selecting the premarket regulatory authorities to be applied to combination products? Is one premarket review mechanism (e.g. premarket approval (PMA), premarket notification (510(k)), new drug application (NDA), or biologic licensing application (BLA)) more suitable than another for regulating combination products?**

Response:

a) Determination of authority for premarket review should include review of localized vs. systemic effects of the product as a part of the primary mode of action. The decision on primary mode of action goes beyond the definition of drug, device, or biologic. The relationship and similarities of the proposed product to other existing products should be considered. By limiting the determination of the authority for

premarket review only the definition of the product it can happen e.g. the delivery of energy (a non-chemical action) for treatment of disease in a localized tissue would be regulated as a device since energy is the primary mode of action for this treatment. However, the delivery of a chemical substance for treatment of the same disease in the same localized tissue would be regulated as a drug since chemical action is the primary mode of action for this treatment. These differing pathways require two very different pre- and post- market mechanisms even though both treatment modes would have similar effect on tissue and disease states. Thus determination of authority should include many aspects of the product beyond simply the definition.

Consistency of review approach should be maintained within all decisions based on previous decisions or a sound rationale for deviation provided.

b) The review mechanism should be assigned based on the lead review division. Additional number of copies of submissions should be provided by the sponsor based on the need of the secondary review division. Consult from other review divisions should be required to occur and required to be performed within the mandated review times of the primary review division. Failure of a secondary review division to meet the requirement of the primary review division deadline should count against the secondary review division's review goals.

4. **Recognizing the need to ensure product safety and effectiveness, what criteria should FDA use to determine whether a single application or separate applications for the individual components would be most appropriate for regulation of a combination product? Should the need to apply a mixed regulatory approach influence whether one application or two are more appropriate?**

Response:
In the case in which one component has been approved for the intended combination use but another component has not, the appropriate premarket application would be the one that pertains to the component not previously approved.

In the case in which none of the components have previously been approved for the intended use, primary mode of action may determine the most appropriate premarket application.

In most, if not all circumstances, we believe that filing two separate premarket applications is NOT necessary to meet safety and effectiveness requirements. One premarket application may address the safety and effectiveness of all product components. There may be business circumstances, however, in which industry deems it desirable to submit two separate premarket applications and this option should remain open. In general, the compilation of more than one premarket application would be particularly burdensome on industry, presumably requiring payment of separate user fees for each application, the compilation of two separate applications, in addition to different review times and centers.

The need for a mixed regulatory approach should be evaluated on a case by case basis and does not need to be the impetus for requiring two separate applications. In the case of a drug/device combination product, the elements of a PMA can be filed as a subsection of an NDA, and an NDA can be filed as a subsection of a PMA. One premarket application can address safety and effectiveness requirements. Primary mode of action alone should determine what type of premarket application is required and which center has primary review.

FDA may consider drafting a guidance document which identifies generic categories or classes of combination devices which historically have required one type of premarket application or another.

5. **What scientific and policy principles should be followed in determining the appropriate manufacturing and quality system regulatory authorities (e.g. Current Good Manufacturing Practices versus Quality System Regulations) applicable to combination products?**

Response:
Both the CGMP and QSR regulations aim to accomplish the same quality endpoint in ensuring patient safety by requiring consistent and reproducible manufacturing control systems. While device QSR design controls are more demanding during the product development process, the drug component CMC and associated drug master file (DMF) can be a daunting—and in some cases—impossible task for a device manufacturer to take on. The drug component of a combination product often has an existing DMF and FDA approval for a specific indication therefore, there does not appear to be any added scientific value for a device company to retrace preclinical or clinical testing that already has been conducted by the drug company.

We recommend that the manufacturer of the combination product should consider the "additive" effect of the new component by looking at the potential impact of the drug on the device and vice versa. In making this determination the manufacturer should consider the safety, effectiveness, and biocompatibility of the combination product utilizing existing QSR design controls processes. The additive effect of merging the drug with the device at the point of the QSR design controls with a manufacturing documentation system to ensure safety, quality, and drug potency would be incorporated into one quality device manufacturing system.

6. **What scientific and policy principles should be followed in determining the appropriate adverse event reporting requirements (e.g., the drugs and biologics adverse event reporting system. Medical Device Reporting) to be applied to a combination product?**

Response:
This would depend on the pathway for approval by the FDA. Therefore, the follow-up regulatory post market reporting system would follow the same pathway from where it is approved. Unless FDA sees a different approach and would specified this in the approval letter, where an adverse event should be reported. It would not be likely that the event

should be reported into both the drug and device reporting system, because they will not be reviewed similarly. If FDA leaves it to the regulated industry, different companies could choose one or another event reporting system and then the same events would not be reviewed equally. There could also be a requirement to have both centers co- review the reported event but the process on how this would be done would need to be detailed in the SOP's for the Center of Combination products.

7. **What other comments do you have concerning other issues related to FDA regulation of combination products? (examples may include cross labeling of products intended to be used together though manufactured by different companies; and application of promotion and advertising policies to combination products)**

Response:

a. Mutual Cross Labeling

Mutual cross labeling should be required in very limited circumstances, for instance where there is data demonstrating hazards if a very specific product is not used as part of the combination. The requirement for mutual cross labeling serves to limit the availability of advances in health care. The costs associated with changing labeling, particularly to a manufacturer for whom the combination may be a small portion of their overall business, often lead to a cessation of development of combination products that would provide significant benefits to patients.

The Agency has a mandate to ensure that products are thoroughly tested for safety and effectiveness and that sufficient instructions and labeling exist so that the products can be used properly. This mandate does not change because a drug and device are used in combination rather than two devices being used in combination. Thus, the standard for cross labeling of combination products should not exceed that for product combinations within one classification of product. In most cases, the Agency's mandate can be accomplished by thorough documentation of how the combination is to be used in the labeling of one component – usually the component marketed by the company that has conducted the testing. Documentation in one set of labeling is consistent with what is usually done for devices indicated for use with other devices.

By definition, a combination product is intended to be used only as a combination. Thus, though the combination may "add" indications to the other component, these indications are only applicable when used as part of the combination. Given that complete instructions for use for the entire combination product are given with one component of the combination, there are no additional needs for labeling of the other component in order to ensure safety and effectiveness of the combination. When the products are used separately, only the indications and instructions necessary for stand-alone use are necessary, not those for the use of the combination.

Thus, the requirement for mutual cross labeling does not significantly add to the safe and effective use of the product, but often adds a significant barrier to market entry.

b. Promotion and Advertising

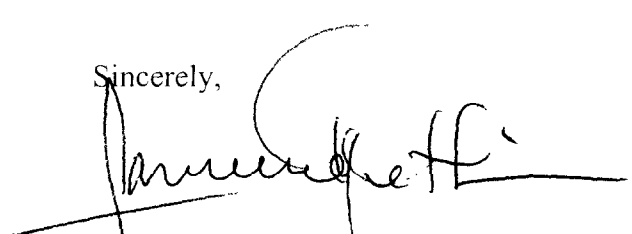
The promotion and advertising of combination products should be consistent with the premarket regulatory authorities applied to the product. Thus, if the product is approved via the PMA process, the promotion and advertising regulations for devices should apply. Similarly, products approved via the NDA process should be subjected to the promotion and advertising regulations for drugs. For combination products that have components regulated by different premarket authorities, such as having both an NDA and a PMA, each component, when marketed as a separate component, should be subjected to their respective promotional regulations. For this category of product, part of the combination device approval process should provide a method for the sponsor(s) and FDA to agree upon how the *complete system* may be promoted. FDA should strive to make consistent decisions regarding promotional regulations for combination products of a similar nature.

c. Communication

The Agency should make the regulatory process for combination products more transparent. Improved communication will facilitate this. For instance, more jurisdictional decisions should be published. These decisions should also provide more details on laboratory test requirements, clinical requirements and the rationale for the decision. Release of guidance documents for more classes of combination devices should be a priority. Guidance documents add clarity and consistency to the data requirements, and lead to more efficient submissions, reviews and approvals.

As technology, innovation, and the desire to provide improved treatments for patients continue to push the boundaries of combination products, AMS supports the Agency's reexamination of their combination product policies. AMS appreciates this opportunity to comment on the issues surrounding combination products that challenge both the Agency and industry.

Sincerely,



Lawrence W. Getlin
Vice President Regulatory, Medical Affairs and Quality Systems
American Medical Systems