



1225 Eye Street NW, Ste. 400  
Washington, DC 20005

August 20th, 2004

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

Re: Docket No. 2004N-0194, Federal Register: May 7, 2004 (Volume 69, Number 89, Page 25527-25533)

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's, the Agency's) Proposed Rule on the Definition of Primary Mode of Action of a Combination Product.

### **General Comments**

BIO strongly supports FDA's effort to improve the transparency and consistency of combination product regulations, and FDA's goal of improving the predictability of the regulatory process for such products. We believe it is very important that FDA continue to assess stakeholder feedback and ensure that any Final Rule on this topic incorporates critical industry concerns related to the regulation of combination products. In general, the selected stakeholder comments previously

received by FDA reflect the basic concerns of BIO member companies, and while we are encouraged by the Agency's response to these points as discussed in the Proposed Rule, we feel that there are several points that warrant additional comment.

## **Specific Comments**

### **Definition of Primary Mode of Action**

The proposed algorithm uses the Primary Mode of Action (PMOA) as the initial point of decision. When PMOA is unclear, the second level of determination would be applied which includes previous jurisdictional decisions as well as available expertise at the particular Centers. As mentioned in the Proposed Rule in the Agency's discussion of input received, BIO shares the opinion of stakeholders that precedent and expertise are very important and should be considered in determinations regarding combination products.

Many BIO member companies have embarked on development plans based on precedents established for existing products and which reflect current working relationships with particular Centers. We believe implementation of the proposed algorithm, in a manner that is inconsistent with previous jurisdictional assignments, could jeopardize many of those projects. Because of the potential for inconsistency between future and past decisions, we strongly recommend the Agency describe, as part of preamble language, how it will address currently approved products and the concern regarding potential inconsistencies that might arise as a result of the application of the Proposed Rule vs. previous decisions.

### **Intended Use of a Combination Product in relation to Primary Mode of Action**

As noted in the Proposed Rule in the Agency's discussion of input received, many stakeholders felt that the definition of PMOA should be based on consideration of the combination product as a whole. BIO also shares this view and believes that the definition of the primary mode of action must take into account the combination product as a whole in order for sponsors and FDA to reliably establish a consistent approach to the regulation of combination products. It is also important, in our opinion, that FDA further clarifies and confirms its reliance on the concept of the intended use of the product as a key determinant in assessing the definition of the therapeutic action of any combination product. Although this principle is cited as an integral part of the Agency's practice in assigning a primary mode of action to combination products for over a decade, further clarification and precision regarding the Agency's interpretation of this principle is still needed. The intended use of a combination product as developed and designated by the sponsor is a critical concept that must be considered in the assignment of the Agency component for purposes of product oversight and related regulatory matters.

### **Definition of Mode of Action of Constituents**

FDA notes in the Proposed Rule that combination products will typically have more than one mode of action, varying according to their composition and relative contributions of their constituent parts. The Proposed Rule then provides a definition for the mode of action of a biological product, device, or drug as currently reflected in the Public Health Service Act or

relevant sections of the Federal Food, Drug, and Cosmetic Act. As incorporated into the assignment algorithm, consideration of each constituent's mode of action according to its individual definition would be the first critical step in determining the most important therapeutic action of the combination product.

As addressed in our comment above regarding the relationship between the intended use of the combination product and the process for assigning the primary mode of action of the product, we feel strongly that consideration must be given to the intended use of the combination product as a whole when assessing and defining the contribution of the constituent parts of that combination product. The Proposed Rule focuses only on the statutory definitions of a biological product, device or drug and does not reflect all of the historical and contextual complexities that have evolved into current practice in the regulation of each of these categories of regulated articles. For example, it is not clear in the Proposed Rule that the assessment of a biological constituent part of a combination product would allow for instances in which the biological constituent functions with a device mode of action, because the Proposed Rule focuses only on the definition of the constituent part. For these reasons, BIO recommends that FDA also consider the intended use of the combination product as a whole and not rely strictly on the statutory definition of each constituent part when assessing a novel combination product. Again, we would suggest that the Agency clarify this point in the Final Rule.

### **Examples of Combination Products**

While it is impractical for FDA to publish an exhaustive listing of all possible examples of combination products, it is worth noting that the combination products cited in the Proposed Rule are relatively straightforward and do not appear to represent significant challenges to the application of the assignment algorithm. In particular, the Proposed Rule does not provide any examples of drug and biological product, device and biological product, or drug, device and biological product combinations. Without any examples of a combination product involving a biological product constituent, it is difficult to fully discern the suitability and appropriateness of the Proposed Rule and the Agency's thoughts regarding these types of combination products. We encourage FDA to address this oversight by engaging in further dialogue with industry and by clarification in the Final Rule.

### **Intercenter Agreements and Related Guidances**

The current Intercenter agreements offer guidance for possible jurisdictional issues. It has been recognized for some time that the agreements are outdated and in need of revision. In fact, in some examples, the agreements would not be consistent with the proposed PMOA regulation. While it may be possible to address intercenter issues as part of the preamble of the Final Rule, BIO believes that an update of the current intercenter agreements should be undertaken, with draft agreements published for comment prior to finalization.

Although the recently published *Draft Guidance for Industry: Combination Products, Timeliness of Pre-market Reviews; Dispute Resolution Guidance* addresses some aspects of the regulatory process for combination products that are not part of the Proposed Rule, we would

recommend that FDA provide additional clarification in the Final Rule on related issues in the following areas:

*?? Regulatory Process vs. Assignment of Center Responsibility*

A combination product with device and drug components may be found to have a PMOA of a drug and thus be assigned, “to the agency component with responsibility...” for drugs. While it may be presumed that the applicable regulatory authority will be clear cut in cases in which the PMOA determination is relatively straightforward, it would be helpful for the Agency to further comment on its intended approach in situations that are potentially more complicated than the examples provided in the Proposed Rule.

*?? Review Timelines and Multiple Submissions*

Existing guidance states that each combination product submission would be reviewed under the specific timelines described for that type of submission. However, this approach does not address the situation in which two separate submissions are required for approval of a combination product, with approval of both components required prior to introduction of the combination product.

BIO strongly suggests that the Agency address this issue and identify a process for coordinating timelines for combination products that involve multiple submissions. We recommend that any approach to this issue be consistent with the concept of least burdensome regulatory pathway, and believe that the Office of Combination Products should take the lead in coordinating such reviews in order to make novel combination products available to the public according to the shortest possible regulatory timelines.

In conclusion, we appreciate the opportunity to provide our comments and look forward to finalization of the Proposed Rule.

Sincerely,



Sara Radcliffe  
Managing Director  
Science and Regulatory Affairs