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0448 '03 JAN 28 A9:19

January 24, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
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SUBJECT: DOCKET NO. 02N-0445
FDA Regulation of Combination Products
Comments from Baxter Healthcare Corporation

Dear Sir or Madam:

Baxter Healthcare Corporation/BioScience Division (Baxter) respectfully submits the following comments in response to the Federal Register Notice Docket No. 02N-0445, dated October 28, 2002, concerning the FDA regulation of combination products. With the recent establishment of the Office of Combination Products (OCP) effective December 31, 2002, we would like to take an active role in assisting the agency with defining the premarket review processes and the postmarket regulation of combination products.

Baxter will comment on the seven questions posed in the subject FR Notice which were addressed by industry representatives at the FDA Public Hearing on Combination Products, held November 25, 2002. The questions are restated below in italics followed by Baxter's comments.

Assignment and Intercenter Agreements

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?***

Comments:

a) To determine the primary review responsibilities for combination medical products, FDA should consider establishing a framework for initial scientific information that evaluates:

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i. The principal intended use of the combination product and

ii. the method by which the principal intended use of the product is achieved (by pharmacological, immunological, or physical means).

b) Furthermore, we believe that the jurisdiction decision should not be driven by the type or origin of materials utilized in the combination product.

c) This review decision would be made by a Review Panel within OCP that is comprised of agency individuals with scientific and clinical expertise representing each of the major reviewing Centers, such as device, drug and biologic. This panel would assume responsibility for assigning the Centers with both primary and secondary responsibility for review of the Combination Product and would clearly define which center has lead responsibility for administrative oversight of project review.

d) The Intercenter Agreements should be standardized and compiled into one comprehensive agreement/process that would be used by OCP to address all combination products regardless of how many Centers are involved in the review (i.e., one, two, or even three Centers). Ideally, no more than two centers should be engaged in a product review, to minimize complexity.

e) Every effort should be made to develop a guideline that minimizes the number of Centers and individuals involved in review and minimizes the level of redundancy involved in the review with respect to reviewers' area of scientific/clinical expertise.

f) The product sponsor would receive a written OCP decision outlining (1) the primary and consulting review Centers, (2) the scope of each Center's premarket and postmarket review and oversight responsibilities, and (3) the lead reviewer name and contact information within each Center. In some respects this process is similar to the current "Request for Designation" process managed by the Chief Mediator and Ombudsman, however it is expected that the OCP designation document will be much more comprehensive in providing direction to the sponsor on how the review and file maintenance process will work throughout the life of the product, as well as the rationale for the decision.

2. ***What factors should FDA consider in determining the primary mode of action of a combination product? 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)?***

Comments:

a) The scientific information that we believe should be assessed by OCP during the initial evaluations of a combination medical product is provided above in response to Question 1, above.

b) In the case of a particularly complex product, if the advisory review panel makes a determination that differs from that of the sponsor, the advisory panel must convene a meeting with the sponsor to discuss their differences.

Marketing Applications

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?***

Comments:

a) The Center with the most applicable expertise given the product's intended function will most likely be the most relevant evaluator of potential patient safety and efficacy given the staff's scientific and clinical expertise.

b) Regardless of format (i.e., NDA, BLA, PMA), the focus should be on safety and effectiveness.

c) We would like to recommend that a single submission filing is desirable, as opposed to "companion" filings for the primary reviewing and consulting centers. This single filing should represent the most efficient, least burdensome approach for the sponsor, and if a harmonized global format exists, such as The Common Technical Document, this should be followed.

d) The format of the submission could be structured in such a fashion as to allow a subpart (or certain volume(s)) to be disengaged from the complete

submission for convenient review by any consulting Center. The administrative process should be centralized within OCP in all cases. Furthermore, this approach would align with the statutory mandates of MDUFMA 2002 that requires OCP to:

i. Ensure timely and effective premarket review of combination medical products

ii. Oversee the timeliness and review coordination among Centers

iii. Ensure consistent and appropriate postmarket regulation of the combination product

e) Early collaborative meetings are to be encouraged between OCP and the sponsor as with current regulatory premarket review processes.

f) The agreement letter issued by OCP to the sponsor should clearly outline the necessary types of data required for each Center and stipulate specific regulations that shall apply if mixed.

g) FDA Combination Product Guidance should be generated based on sound scientific principles for the conduct of preclinical, clinical, safety and toxicity studies, CMC and stability programs. In particular, the approach taken for Combination Products should be developed with the intent of harmonizing, as much as possible, the study design criteria that is typically applied by each of the three reviewing centers..

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 individual components would be most appropriate for regulation of a combination product? For example, FDA may determine that it is necessary to apply elements of different regulatory authorities to a combination product to ensure safety and efficacy (e.g., device postmarketing reporting for the combination product, with drug current good manufacturing practices (CGMPs) applicable to the drug component only). Should the need to apply a mixed regulatory approach influence whether one application or two are more appropriate?***

Comments:

a) Baxter does not believe that a "mixed regulatory approach" should automatically require multiple premarket applications and parallel post-market reporting to multiple Centers. Each submission must be regulated in a way that allows the sponsor to conduct business via the most transparent and least burdensome, straightforward administrative processes. As stated in item

1(b) above, a choice should be made as to which Center assumes responsibility for each element of the pre- and post- market review process. For example, either an AER or MDR format for pharmacovigilance may be required, but not both. See also suggestions in response to Question 3.

Other Issues:

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 Regulation) applicable to combination product?***

a) OCP should utilize the guidance/regulation that would permit the appropriate manufacturing and quality system requirements to be maintained for all components in their place of manufacture. Since the components are likely to be utilized in other non-combination products, it makes sense to utilize the GMP requirements that currently apply to each component. For example, design controls would apply to the development of a device component of a drug-eluting stent. Likewise, the manufacture of the drug component would be subject to parts of 21 CFR 211.

b) For a GMP inspection, the agency should be attentive to the need to ensure a consistent and relevant inspection if multiple facilities are involved. Redundant inspection should be avoided. For example, if two components of a combination product are manufactured in device and biologic facilities respectively but the final combination product is assembled in the device facility, then the device facility should be inspected per device requirements. Likewise, the facility manufacturing the biologic component would be inspected in accordance with 21 CFR 211.

c) For pre-approval inspections, the combination products program should be well defined within the OCP and would draw on a pool of appropriately trained individuals qualified to address, in a team approach, the various combinations. We suggest that if one or more of the components is already licensed, cleared or approved under a separate filing, that inspection of the manufacturer of said component(s) could be waived if the facility has been inspected within the last two years and is considered by the agency to be in good standing.

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

Comments:

a) This decision would again relate back to the primary intended function of the product. If, for example, the primary mechanism is pharmacological, it would be likely that the lead center would be the custodian of the adverse event database. To avoid confusion, only one center (that is, the primary center) should assume responsibility for receiving adverse event reports for the product. If expertise from another center is required, this consultation should be handled internally by a defined FDA procedure and should not have to be managed by the sponsor. If a secondary center is asked by the lead center to consult on an adverse event, there is no reason why this situation should not be made visible to the sponsor. As stated in 4a, a clear assignment must be made for post market reporting requirements.

b) In any case, the manufacturer must ensure that adequate expertise and appropriate investigational procedures are in place to evaluate adverse events regardless of the reporting format, recognizing that the manufacturer is obligated to investigate and carry out corrective action without respect to the applicability of Quality System Regulation (QSR) or GMP.

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

Comments:

a) We believe that applicability of promotion and advertising policies should be the responsibility of the relevant support staff in the primary reviewing center. For example, if the lead review center is CDER, then DDMAC will oversee promotional practices.

In conclusion, we hope that in developing the combination products program, that FDA will take the opportunity to maximize the harmonization of policies and practices existing at the three key reviewing centers.

Baxter Healthcare appreciates the opportunity to comment on these issues. If you would like to discuss these comments in further detail, please contact Arlene Vidor at 818-507-5566 or Lori DonDiego at 510-818-4644.

Sincerely,

Lori DonDiego for

Arlene Vidor
Vice President, Regulatory Affairs
Baxter Healthcare Corporation

CC: Lori DonDiego