From: Berbakos, Elizabeth G [mailto:Elizabeth.Berbakos@fda.hhs.gov]
Sent: Thursday, June 25, 2009 1:11 PM
To: Aguilar, Brenda; Matsuoka, Karen Y.; Malanoski, Margaret A.
Cc: Lutter, Randall; Boocker, Nancy; Axelrad, Jane A; Presley, Denver; Capezzuto, JonnaLynn
Subject: FW: Antimicrobials

Karen/Brenda, please see the attached response to your questions on the Antimicrobials Guidance.

Liz

<<OMB Response 062409.doc>>

1) The PRA requires agencies to solicit comment on, among other things, "ways to enhance the quality, utility, and clarity of the information to be collected."

FDA Response:

We believe that the comments identified below refer to policy issues rather than paperwork burdens. None of these comments specifically mentioned the information collections or paperwork burdens. We also note that none of these comments on the guidance explicitly questioned the practical utility of the ICR. No comments were submitted in response to FDA's 30-day PRA Notice, so we do not believe these comments identified by OMB were PRA-related.

A -- **Wyeth specifically requested clarification on reporting option IV.C. (see page 5).**

FDA Response:

Application holders for systemic antibacterial products should have the expertise to properly meet the requirements for maintaining the susceptibility test interpretive criteria (breakpoints) in the labeling of their approved products. The type of information that an application holder might submit will depend upon the scientific basis for why the firm believes that the standard does not apply to its drug product. FDA expects an application holder to articulate its scientific rationale for why the standard would not apply and no labeling change is needed. This type of scientific assessment and reasoning is commonly provided throughout the New Drug Application process.

In addition, FDA intends to issue a separate guidance document with recommendations on the scientific issues associated with updating susceptibility test interpretive criteria. This guidance was intended to address procedural issues of how FDA will comply with the Congressional mandate in section 1111 of the Food and Drug Administration Amendments Act (FDAAA). We believe this separate guidance will provide the level of detail requested by Wyeth.

B -- **Wyeth also suggested that the utility of the information collection could be improved—and burden reduced—if FDA were more clear about why FDA decided to adopt any particular standard. I quote: "We believe that recognition of a standard by publishing in the FR does not appropriately communicate revisions or updates to the standard and places an undue burden on the application holder to identify and assess each change. Communication of this information is necessary for the application holder to make a timely and accurate assessment of the label, determine if a labeling update is needed, provide justification for not making a label change, or justification to accept an alternate standard."**

"Determine if a labeling update is needed" is burden associated with option IV.C. "Provide justification for not making a label change" is IV.C.

FDA Response:

We disagree that we are placing an additional burden on application holders. All application holders are under a continuing obligation to update their labeling "when new

information becomes available that causes the labeling to become inaccurate, false, or misleading" (21 CFR 201.56(a)). Thus, application holders should be independently reviewing their records, published literature, and the actions of nationally and internationally recognized standard setting organizations, to determine whether the susceptibility test interpretive criteria for their drug products is up to date. This guidance provides a less burdensome alternative of relying on an FDA-recognized breakpoint to update labeling. Without this guidance, the application holder would still have to evaluate whether its labeling needs updating.

We note that nationally and internationally recognized standard setting organizations generally have an open process for updating their standards. The information considered in this process should provide adequate information about the need to update labeling. In addition, prior to the first FDA recognition of breakpoints, we intend to request input from an Advisory Committee, which will be a public process.

2) The PRA requires agencies to solicit comment on the "accuracy of FDA's estimated burden..."

Hospira indirectly commented on the burden associated with assessing which reporting option (including the option of not changing the labeling at all). Hospira does not cite IV.C., but it is clearly implied. The comment reads as follows:

"The process for the evaluation of the published standards would first include an assessment of the changes to determine whether the published standards should be accepted (approach IV.B.1) or whether the applicant chooses to maintain the current standard used in their application or another standard not recognized by the Agency (Approach IV.B.2). Either scenario would most likely exceed the 60 days suggested by the Agency...."

Again, Hospira does note cite IV.C. but the "or whether the applicant chooses to maintain the current standard used in their application" is option IV.C. Therefore, it is relevant to this collection.

FDA Response:

Hospira's comment does not mention the accuracy of FDA's estimated paperwork burden (i.e., it does not take issue with the estimated 16 hours to prepare a submission explaining why a recognized breakpoint does not require updated labeling). This comment applies to a policy issue regarding the timing of when an application holder should submit its updated labeling or its explanation why no update is needed. As the guidance explains, all application holders are under a continuing obligation to update their labeling "when new information becomes available that causes the labeling to become inaccurate, false, or misleading" (21 CFR 201.56(a)). If the labeling is false or misleading in any particular, a drug can be deemed misbranded. The guidance is merely a recommendation about how quickly an application holder should update its labeling.

We note that we have revised the guidance to recommend that application holders make their submission within 90 days of FDA recognizing a standard. We disagree with Hospira's argument that it would most likely exceed 60 days suggested by the Agency to decide whether to update labeling. It is important to remember that FDA recognition of a

standard will occur after a standard setting organization has adopted and published a new standard. Generally, this is a lengthy process where the standard setting organization considers scientific evidence for a new standard at a meeting and then adopts the standard at a following meeting many months later. During this period an application holder has more than adequate time to consider whether the scientific evidence is appropriate for its drug product.

3) The PRA requires agencies to solicit comment on "ways to minimize the burden of the collection of information on respondents..."

Almost every commenter said that it is burdensome to have to keep searching the FR to see if FDA published updated standards. Since learning about the FR notice is the trigger for any of the 3 reporting options—including IV.C—this is a relevant comment. In fact, Merck specifically identifies this comment as pertaining to option IV.C: "The Draft Guidance seems to suggest that marketing application holders will learn about and react to recognized standard when published in the FR. A described in the Draft Guidance, we believe that is a reversal of the process. It would be a significant burden to mobilize internal resource to put together and submit a labeling supplement to meet the 60 [calendar] day deadline form publication of a recognized standard. We believe a more direct process would be for the agency to first notify appropriate antibacterial application holders with sufficient time to respond prior to FR publication."

These commenters suggested a specific alternative. FDA should address the alternative.

FDA Response:

As explained in our response to question 2, applications holders currently have an ongoing obligation to update their labeling and monitor scientific information regarding their drug products. By issuing an FR Notice recognizing breakpoints, we are helping these application holders. The FR Notice gives them the option to significantly reduce the burden of providing scientific information to support their proposed labeling changes. In addition, they should know about the possible need to update an individual drug product's labeling well before FDA issues its FR Notice because they can monitor the standard-setting process.

We disagree that it is a significant burden to for an application holder to look for notification in an FR Notice. One purpose of the Federal Register is to provide notice to interested parties of government regulatory actions. This mechanism developed generally to avoid the burden on government agencies to notify each potential regulated entity and the general public of its proposed or final regulatory actions. In addition, FDA's website will also make the FR Notice publicly available.

4) Comments regarding the information collection requirements but covered under different ICRs

These comments should be acknowledged and the response should be something to the effect that they are covered under different OMB control numbers. To the extent that the comments suggest that the burden estimates for those ICRs are

not accurate or the utility of those ICRs could be improved, FDA should state that FDA will revise the estimates or improve the utility of those ICRs when they next come up for renewal.

FDA Response:

We will address those comments, to the extent necessary and appropriate, when we propose 0910-0572 and 0910-0001 to OMB for extension of the approvals.