From: Lutter, Randall [mailto:Randall.Lutter@fda.hhs.gov]
Sent: Wednesday, June 03, 2009 1:17 PM
To: Neyland, Kevin F.
Subject: RE: Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

Here are our comments about whether the public comments that you have flagged are really "related to" the ICR. While we do not agree on whether the noted comments are "related to" the ICR, it is also not clear to me that this is the right test. You should know that the total burden from the guidance is 32 hours per year, according to our estimate.

Please take a look and let me know when would be a good time to talk.

-rl

From: Neyland, Kevin F. [mailto:Kevin_F._Neyland@omb.eop.gov]
Sent: Wednesday, May 27, 2009 6:21 PM
To: Lutter, Randall
Subject: Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

Randy,

Following up on our phone call and emails, I asked staff to show me comments on guidance that were essentially comments on an ICR.

They skimmed 6 of 10 comments related to the draft guidance "Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices," located on Regulations.gov, and found at least one reference related to the ICR in each of the comments. The comments seem to be along the following themes: a) the guidance is unclear as to what info is required for the annual report, b) the timeframe is too short to justify label changes, and c) the timeline for FR submission is too long to allow those interested to disseminate findings.

For your convenience, the 6 skimmed letters are attached w/ marginalia. Do you agree that the noted comments are related to the ICR? Let's talk soon so that we can move forward.

Best!

Kevin

FDA Comments

OMB has provided examples of comments to the draft guidance "Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices," that OMB asserts relate to the ICR. Below we discuss individually each comment that OMB identified as "related". We note that 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.

We also think it is important to remember a few key points related to this guidance.

- First, FDA's existing regulations require application holders to update drug product labeling, submit labeling supplements, and submit annual reports. OMB has already approved the paperwork burdens associated with these regulations, which are the significant information collections referenced in the guidance.
- Second, the total industry-wide estimated annual reporting burden for the new collection identified in the guidance is 32 hours.
- We also remind OMB that guidances are not binding. Sponsors may follow the guidance or they may use alternative methods of complying with the regulations, though these may be more burdensome. We believe the burden of following the guidance's option of relying on recognized interpretive criteria for susceptibility tests would be significantly less than the burden for alternative means of complying by submitting data to update the labeling of individual drugs to reflect new susceptibility test interpretive criteria.

More important, in delaying this guidance, we are delaying an important public health initiative that is mandated by the Food and Drug Administration Amendments Act of 2007 (FDAAA). Updating susceptibility test interpretive criteria (breakpoints) in drug and device product labeling is important to ensure that physicians are using accurate information in making clinical decisions about appropriate therapies to treat bacterial infections. The increasing prevalence of drug resistant bacteria (such as MRSA) makes this information critical. Although drug sponsors have an obligation to keep their labels up to date, FDA has identified a large number of antibacterial drug products with out of date labeling. Congress recognized this problem and in section 1111 of FDAAA, Congress mandated that FDA update and publish breakpoints for antibacterial drug products.

The guidance describes a new process that meets the mandate of Congress, but is less burdensome for both FDA and drug sponsors. Under the new process, rather than each sponsor individually gathering data to support updated breakpoints and submitting this information to FDA for individual review, FDA will recognize standards for breakpoints from a nationally or internationally recognized standard setting organization. Drug sponsors will be able to rely on these recognized standards to update labeling and fulfill their statutory and regulatory requirements. FDA will be able to review the information

more quickly because we will have recognized a standard. Under an alternative approach, if a sponsor does not agree with a recognized standard, it has the option of submitting a labeling supplement with adequate supportive data. Under a second alternative approach, when an application holder's label differs from a recognized standard and the application holder believes no change is needed, the application holder can submit a letter justifying its position. It is only for the third case, which FDA anticipates will happen very infrequently (possibly twice per year), where we have asked for OMB approval of a new information collection. It is difficult to understand how concerns about this annual aggregate reporting burden of 32 hours should delay a guidance that will save both FDA and industry many hundreds of hours while benefiting public health.

AstraZeneca Comments Identified

Please clarify if prior approval supplements already approved and/or a prior approval supplement under review should be identified in the NDA/ANDA annual report.

It will be helpful to the application holder if the agency can specify what microbiology data they want included in the NDA/ANDA annual updates, e.g., surveillance data, PO data, etc. and level of detailed information generated inside and outside the US.

FDA Response to OMB

We disagree that this comment addresses a proposed information collection in the guidance. OMB has already approved the information collection for annual reports under control number 0910-0001 (the requirement in 21 CFR 314.81(b)(2)(i) to include in the annual report a brief summary of significant new information from the previous year that might affect the labeling of the drug product). We also believe that the guidance and its reference to the annual report regulation make clear that sponsors are required to provide only a "brief summary" in the annual report about whether their breakpoints are current or need updating and what actions have been taken or will be taken in light of any new information.

Cubist Comment Identified

Unless standard-setting organizations act in close harmony with an annual FDA schedule and promulgate standards accordingly, the annual publication could serve as an artificial timeline that ultimately obstructs the speedy dissemination of important findings. We urge FDA to adopt a more flexible approach and recognize and publish in the *Federal Register* any significant new standards or changes in standards, and updates to susceptibility test information, whenever such relevant changes or updates are made.

FDA Response to OMB

We do not see how this comment relates to any information collection in the guidance. The commenter urges FDA recognize standards more frequently than an annual FR

Notice. The commenter does not appreciate that standards are only published periodically and FDA can time the annual recognition of standards to follow publication by an appropriate standard setting organization. Applicants already have and will continue to have the ability to submit a labeling supplement at any point in time to keep their labeling up to date as is required under FDA regulations (21 CFR 201.56(a)(2)) should scientific information arise that warrants a label change. We note that OMB has already approved the information collections (control number 0910-0572) for labeling supplements submitted pursuant to this regulation.

Hospira Comment Identified

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.I) 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).

FDA Response to OMB

This comment does not address an information collection in the guidance. It is focused on the timetable that FDA recommended in the draft guidance for updating labeling after new information becomes available because FDA has recognized a new standard. The requirement to update labeling is found in FDA regulations (21 CFR 201.56(a)(2)). OMB has already approved the information collections (control number 0910-0572) for labeling supplements submitted pursuant to this regulation. We also note that the final guidance recommends 90 days after recognition of a standard for an application holder to update labeling rather than the 60 days described in the draft guidance.

Merck Comments Identified

It is unclear what the review entails and what needs to be reported with the annual report.

As written, sponsors are uncertain regarding what data elements to include in the annual report and we recommend that more guidance be provided in the document.

FDA Response to OMB

We do not believe these comments relate to a proposed information collection in the guidance. The first comment is in response to a recommendation that sponsors review their product labeling at least annually to make sure the breakpoints are up to date and their labeling meets requirements in FDA regulations. Both comments discuss submissions as part of an annual report. OMB has already approved the information collection for annual reports under control number 0910-0001 (the requirement in 21 CFR 314.81(b)(2)(i) to include in the annual report a brief summary of significant new information from the previous year that might affect the labeling of the drug product). We also believe that the regulation is clear that sponsors are required to provide only a

brief summary in the annual report about whether their breakpoints are current or need updating.

Sanofi Aventis Comment Identified

If the labeling is to be updated annually with timelines dependent on the Federal Register notice, would it be possible to do this exercise only one time and not in addition for each open IND?

FDA Response to OMB

We do not understand this comment from Sanofi because the guidance does not discuss updating any information in an IND. The guidance pertains only to updating labeling for approved drug products. Therefore, we disagree that this comment relates to a proposed collection of information in the guidance. We note that OMB has already approved the information collections for labeling supplements under control number 0910-0572 (the requirement in 21 CFR 201.56(a)(2) to update labeling when new information becomes available that causes the labeling to become inaccurate, false, or misleading) and control number 0910-0001 (the requirement in 21 CFR 314.70(b)(2) to submit labeling changes in the product's labeling).

Wyeth Comment Identified

More definitely, we would like to restate our comment in I.B., and recommend that the guidance be revised to focus on (1) how FDA will identify and periodically update susceptibility test criteria for antibacterial products, (2) how FDA will make these findings publicly available, and (3) recommendations regarding the submission of labeling.

FDA Response to OMB

We disagree that this comment addresses a proposed information collection in the guidance. The comment recommends policy changes unrelated to the information collection concerning the overall policy on updating susceptibility criteria. To the extent that the comment discusses the submission of labeling, we note that OMB has already approved information collections for labeling supplements under control number 0910-0572 (the requirement in 21 CFR 201.56(a)(2) to update labeling when new information becomes available that causes the labeling to become inaccurate, false, or misleading) and control number 0910-0001 (the requirement in 21 CFR 314.70(b)(2) to submit labeling changes in the product's labeling).