From: Neyland, Kevin F.
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They skimmed 6 of 10 comments related to the draft guidance "Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices," located on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

Hospira

Date: JUL 29 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852
Electronic submittal to http://www.regulations.gov

RE: Docket No. FDA-2008-D-0339
Draft Guidance for Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

Dear Madam/ Sir:

Hospira, Inc. (Hospira) hereby submits the following comment/clarification request to Docket No. FDA-2008-D-0339, Draft Guidance for Updating Labeling for Susceptibility TestInformation in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices. Hospira is responding to the NOTICE for COMMENTS published on June 12, 2008.

Should you have any questions or require additional information, please contact the undersigned.

Sincerely,

Jean Kirkeleit Davis 7/29/08

Jean Kirkeleit Davis
Official Correspondent/US Agent
Hospira, Inc.
275 North Field Drive, H2
Lake Forest, Illinois 60045-5046
Phone: 224-212-4688
Fax: 224-212-5401
Email: jean.kirkeleitdavis@secure.hospira.com

CUBIST

organizations."[1] Congress, however, recognized the critical importance of timely and up-to-date data by enacting section 1111 of the Food and Drug Administration Amendments Act (Pub. L. 110-85).

Considering the difficulty in treating the bacteria at issue and public health implications of antimicrobial resistance, annual review may not be sufficient to ensure the timely recognition and dissemination of the latest, most appropriate data to healthcare professionals and institutions. 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.

INFO COLLECTION?

II. FDA Should Recognize More Diverse Nationally and Internationally Recognized Standard Development Organizations.

The Draft Guidance states that FDA intends to recognize standards "developed by one or more nationally or internationally recognized standard development organizations."[2] However, no clarification is provided as to the nature or identity of the relevant standard development organizations. It is possible, but undesirable, to infer from the example given of the National Library of Medicine, as the method by which FDA would disseminate relevant standards, that FDA intends to limits its understanding of "recognized standard development organizations" to mean governmental or quasi-governmental entities.

Based on our experience in this field, we strongly encourage the agency to recognize other private or nonprofit entities, including such organizations as the Clinical Laboratory Standard Institute (CLSI), the Infectious Diseases Society of America (IDSA), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), as relevant organizations that are commonly recognized by clinicians and the public health community as "nationally or internationally recognized standard development organizations". We believe clarifications of this kind would greatly enhance the utility of the Draft Guidance.

[1] FDA, Draft Guidance for Industry: Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices, 4 (June 2008).

[2] Id.

CUBIST

0588 8 AUG 13 A11:39

August 11, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane—Room 1061
Rockville, MD 20852

RE: **FDA-2008-D-0339: Draft Guidance for Industry on Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices.**

Dear Sir or Madam:

I am pleased to submit comments to the Draft Guidance on susceptibility labeling in antibacterial and antimicrobial products. Cubist Pharmaceuticals is a leading biopharmaceutical company focused on the research, development and commercialization of pharmaceutical products that address unmet medical needs in the acute-care environment. Headquartered in Lexington, Massachusetts, we currently market CUBICIN® (daptomycin for injection), the first intravenous (IV) antibiotic from a class of anti-infectives called lipopeptides.

CUBICIN received FDA approval for the treatment of complicated skin and skin structure infections caused by certain susceptible strains of Gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus* (*S. aureus* or MRSA). CUBICIN is also approved in the U.S. for the treatment of *S. aureus* bloodstream infections (bacteremia), including right-sided endocarditis caused by MRSA, and is the only IV antibiotic approved for this indication based on the results of a prospective, randomized, controlled registration trial.

I. The Draft Guidance Proposes to Recognize Susceptibility Test Interpretative Criteria by Publishing *Annually* the Standards Developed by Recognized Standard Development Organizations; Recognition Should Come More Frequently as Warranted.

The Draft Guidance states that the FDA recognize susceptibility test interpretive criteria by "publishing annually in the *Federal Register* notice certain standards developed by one or more nationally or internationally recognized standard development

65 Hayden Avenue, Lexington, MA 02421 P 781.860.8660 F 781.861.0566 www.cubist.com

FDA-2008-D-0339

C

sponsors are ultimately responsible for collecting and reporting data, an Agency initiative such as inclusion of more details regarding study design, data collection, and analyses in its Guidance for Labelling for Susceptibility Test Information will help both standard development organizations and sponsors.

Lines 166-170: "*...the differences should be specifically evaluated by the applicant (§201.56(a)(2)). Not later than 60 days after FDA publicly recognizes a standard that is relevant to the application holder's product, the application holder should submit updated labeling (see section III.B) or provide a written explanation why it believes the standard is not applicable to its antibacterial drug product (see section III.C).*"

Recommendation: The correct cross-references appear to be "IV.B" and "IV.C," respectively.

Lines 166-170, 206, 228: "*Not later than 60 days after FDA publicly recognizes a standard... the application holder should submit updated labeling or provide a written explanation....*"

Recommendation: It seems that the timeframe of 60 days could be too short to comply with quality controls and/or provision of scientific justification.

- Would it be possible for FDA to inform the holder in advance of the public recognition, especially if CLSI standards are not judged as appropriate by the FDA?
- Would it be possible to know on which usual date the annual FDA notice will be published in the *Federal Register*?

Line 238: "*Application holders should also include in their annual report....*"

Recommendation: If the labelling 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?

INFO COLLECTIO 2

Sanofi-aventis appreciates the opportunity to comment on this guidance and is grateful for your consideration.

Sincerely,

Brian E. Harvey

Brian E. Harvey, M.D., Ph.D.
Vice President
Regulatory Policy

SPECIFIC COMMENTS:

Lines 57-59: "*The numerical values generated by susceptibility testing to determine whether a particular microorganism is susceptible to a particular antimicrobial drug — the antimicrobial susceptibility test interpretive criteria — are commonly referred to as* breakpoints."

Recommendation: It is suggested that the wording be rephrased. Indeed the breakpoints will be indicated in the labelling for interpretation of the test; the purpose of the guidance is not to describe how the breakpoint is defined, therefore we suggest that "discriminating" should be added, and that "generated" should be replaced in the text by "used." In addition, we understand that the text should be more general and not only refer to the concentration. We propose that the text add in brackets examples of discriminatory values (i.e. concentration, inhibition zone diameter):

> *"Antimicrobial susceptibility test interpretive criteria — commonly referred to as breakpoints — are discriminating numerical values (i.e. concentration, inhibition zone diameter) used in the interpretation of results of a well standardized susceptibility test to define isolates as susceptible, intermediate, or resistant to a particular antibacterial drug."*

Lines 60-62: "*The antimicrobial susceptibility test interpretive criteria can be used to interpret results from either manual or automated AST devices.*"

Recommendation: The Minimum Inhibiting Concentration (MIC) is seen as the gold standard for assessing an antibiotic's potency, but is a crude measure with limitations. However, all other susceptibility test methods should be validated against an MIC determined by a standard methodology. Suggested text is as follows:

> *"The antimicrobial susceptibility test interpretative criteria, commonly referred to as* breakpoints, *are defined for a given method and should be redefined for other methods so that the interpretation given by the alternative method is evaluated as equivalent to the one given by the reference method."*

Line 140: "*...FDA intends to recognize susceptibility test interpretive criteria, associated test methods and quality control parameters, by publishing ...certain standards developed by one or more nationally or internationally recognized standard development organizations.*"

Recommendation: Susceptibility test interpretive criteria are pharmacodynamic criteria included in labelling. Sponsors would benefit from clearer guidelines. For example, for the approval of new drugs, expectations for study design, data collection, and analyses are included in the Agency's Guidance for Industry documents.

The draft Guidance states that the Agency may depend on standards developed by other organizations. However, the final decision may be driven by the Agency's own standards. Since

sanofi aventis

Because health matters

August 7, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2008-D-0339

Draft Guidance for Industry on Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

Dear Sir/Madam:

Sanofi-aventis U.S., a member of the sanofi-aventis Group, welcomes the opportunity to comment on the above-referenced draft guidance entitled "Draft Guidance for Industry on Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices."

This draft guidance informs industry of how the FDA intends to comply with section 1111 of the Food and Drug Administration Amendments Act (FDAAA), which requires FDA to identify and periodically update susceptibility test interpretive criteria for antibacterial drug products and to make those findings publicly available.

GENERAL COMMENTS

The Minimum Inhibiting Concentration (MIC) determined using a standardized method (i.e. CLSI) is seen as the gold standard for assessing antibiotic potency. Other susceptibility methods should be validated against a standardized MIC methodology. A breakpoint is a discriminating numerical value (i.e. concentration, inhibition zone diameter) used in the interpretation of results of a well standardized susceptibility test to characterize isolates as susceptible, intermediate, or resistant. Breakpoints are dependent on the methodology used, and should be defined specifically within a specific standardized methodology. A bacteria isolate designated as 'susceptible' should clinically respond to the usual dose of the antibacterial agent. A 'resistant' isolate should not respond, and an 'intermediate' one may or may not respond to standard doses, yet would have an increased chance of responding to a greater dose if the infection is at a site where the antimicrobial is actively concentrated. As CLSI standards and guidelines are developed through a consensus process on good practices involving the health care community, we would recommend that the information given in the antibacterial labelling follow, when available, CLSI standards, breakpoints, and quality controls guidelines.

sanofi-aventis U.S., Corporate Regulatory Affairs Office, 4520 East West Highway, Suite 210, Bethesda, MD 20814
Tel: (301) 771-1261 www.sanofi-aventis.us

Line #/Section/Page	Original Text	Comment with Rationale / Proposed Change
201-202/IV B2/6	*Updating Through Submission of Information that Supports Labeling Different from a Standard Recognized by FDA*	It is unclear from the Draft Guidance what appeals process is in place in the event that the Agency does not approve the submitted labeling information. Conversely, if the Agency approves the information submitted based on data different from a standard recognized by the Agency, it is unclear if the Agency plans to rescind the prior recognized standard.
238-240/IV D/6	Application holders should also include in their annual report an assessment of whether the information in the *Microbiology* subsection of their product labeling is current or changes are needed (21 CFR 314.81(b)(2)(i)).	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.
270-271/V/7	**UPDATING SUSCEPTIBILITY TEST INFORMATION FOR IN VITRO DIAGNOSTIC AST DEVICES**	As pointed out earlier for drug product application holders, we believe the Agency first should notify appropriate device manufacturers and give them sufficient time to respond prior to Federal Register publication.

INFO COLLECTION

Line #/Section/Page	Original Text	Comment with Rationale / Proposed Change
156-157/IV A-C/5-6	**UPDATING SUSCEPTIBILITY TEST INFORMATION IN ANTIBACTERIAL DRUG PRODUCT LABELING**	The Draft Guidance seems to suggest that marketing application holders will learn about and react to recognized standards when published in the Federal Register. As 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 from 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 Federal Register publication.
161-164/IV A/5	Holders of new drug applications (NDAs) and those abbreviated new drug applications (ANDAs) that are designated as a reference listed drug (RLD), for systemic antibacterial drug products should review their product labeling at least annually $_3$ valuate whether the *Microbiology* subsection is up to date.	We recommend that the guidance specify what the annual labeling review should entail. Holders of marketing application for antimicrobial drugs routinely undertake long term prospective antimicrobial resistance surveillance. It is unclear what the review entails and what needs to be reported with the annual report. INFO COLLECTION
166-170/IV A/5	Not later than 60 days after FDA publicly recognizes a standard that is relevant to the application holder's product, the application holder should submit updated labeling (see section III.B) or provide a written explanation why it believes the standard is not applicable to its antibacterial drug product (see section III.C).	We recommend that the guidance specify what the Agency will want us to respond to. In other words, what dataset will the Agency accept, given the hierarchy of evidence in applying susceptibility interpretive criteria (in vitro MICs, Monte Carlo simulation, and/or clinical isolates from cases of treatment failures). Nonetheless, should the guidance recommend Monte Carlo simulation, we wish to point out that no universally acceptable performance standard exists for method.

Attachment

Docket No. FDA–2008–D–0339; Draft Guidance for Industry: Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

Line #/Section/Page	Original Text	Comment with Rationale / Proposed Change
140-143/III/4	Where appropriate, FDA intends to recognize susceptibility test interpretive criteria, and associated test methods and quality control parameters, by publishing annually in a *Federal Register* notice certain standards developed by one or more nationally or internationally recognized standard development organizations.	We recommend that the guidance specify the standard development organization. Currently, the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are the most established international standard development organizations for antibacterial susceptibility interpretive criteria. Indeed, standards developed by these organizations are not only routinely adopted by antibacterial drug sponsors and susceptibility testing device manufacturers, they are accepted by regulators in many countries and regions. We believe the guidance should specify these two organizations while making room to accommodate others in the future. **Proposed Change** Where appropriate, FDA intends to recognize susceptibility test interpretive criteria, and associated test methods and quality control parameters, by publishing annually in a *Federal Register* notice certain standards developed by one or more nationally or internationally recognized standard development organizations **such as the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).**

guidance and clarity for updating labeling information regarding antimicrobial susceptibility test interpretive criteria, associated testing methodology, and quality control parameters as well as ensure consistent labeling of antimicrobial susceptibility testing (AST) devices. We agree that consistency between interpretive criteria in drug product labeling and those in AST device labeling could promote safe and effective use of the products. We believe a major key to achieving the intended objective of the guidance will be timely communication with marketing application holders and device manufacturers prior to publication of a recognized standard rather than have them react to such published information. Moreover, since the Draft Guidance is silent on antifungal interpretive criteria, associated methods, and quality control parameters, we recommend these specifically be addressed in the guidance.

Specific Comments

In the following table (Attachment), we provide specific comments on sections of the Draft Guidance. In the left column of the table, we identify the line number, sections, and page number in the Draft Guidance; the middle column contains the original text of the Draft Guidance, and the right column carries the key comments and rationale to support our position as well as our suggested changes, where applicable (single strikeout for deleted text and bold/underlined type for added text). See Attachment for more details.

We appreciate the opportunity to share our comments with respect to the Draft Guidance on "Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices." For further information or questions, please contact me by phone 202 508 4567 or email ekopimo_ibia@merck.com.

Sincerely,

Ekopimo Ibia, MD, MPH
Director
Global Medical and Regulatory Policy

Attachment enclosed

Ekopimo Ibia, M.D., M.P.H.
Director
Global Medical & Regulatory Policy

Merck & Co., Inc.
601 Pennsylvania Avenue, NW
North Building, Suite 1200
Washington DC 20004
Tel 202 508 4567
ekopimo_ibia@merck.com

August 7, 2008

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

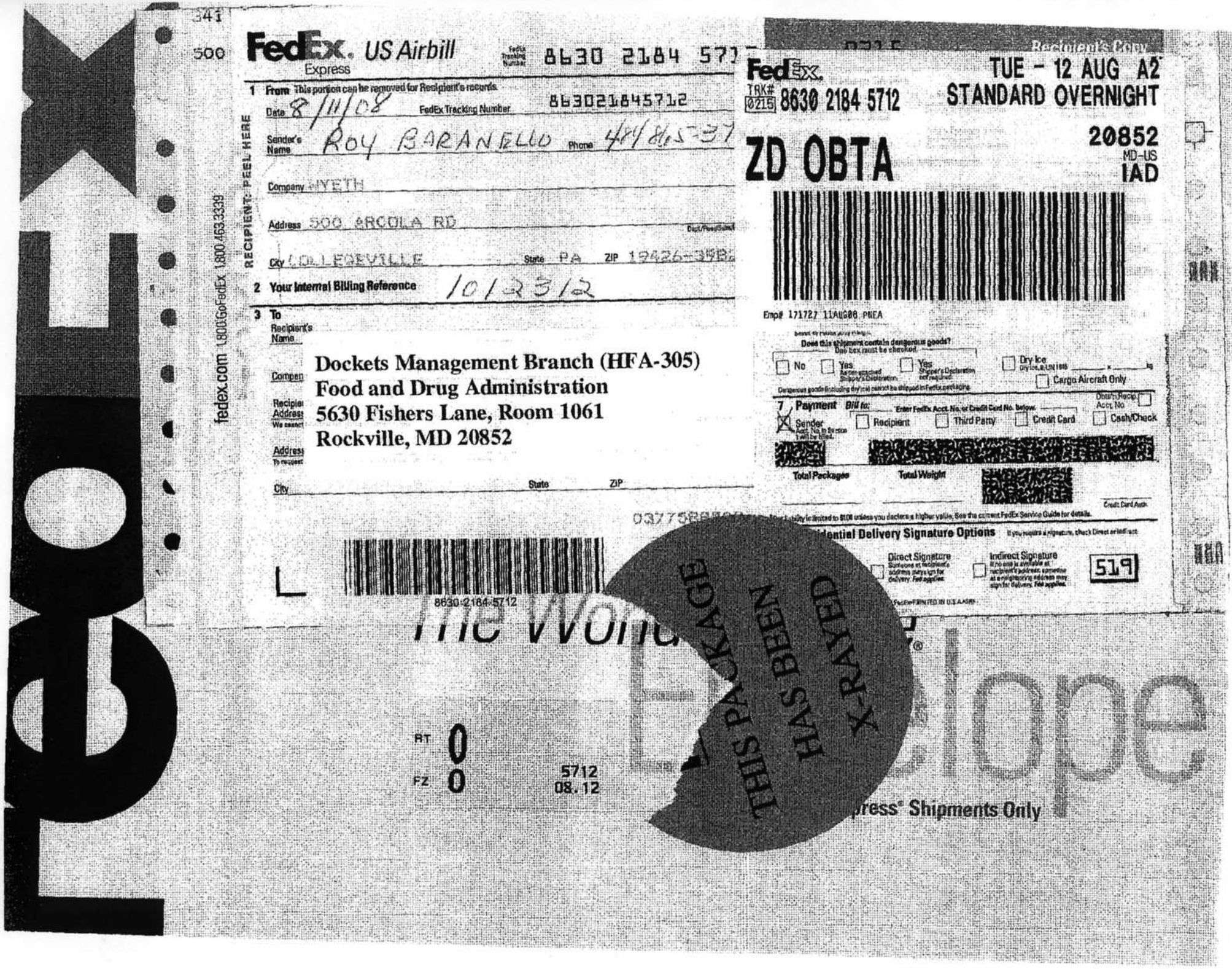
RE: Docket No. FDA–2008–D–0339
Draft Guidance for Industry: Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

Merck & Co., Inc. is a leading worldwide human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing Merck drug and biological product candidates through developmental testing, clinical trials, licensure, and marketing, Merck has acquired extensive experience in antimicrobial susceptibility testing methodology and quality control. We have utilized that experience to author the comments below.

General Comments
We commend the Food and Drug Administration (the Agency or FDA) for its commitment to foster innovation while serving the public health needs of American citizens. We thank the Agency for the opportunity to comment on the "Draft Guidance for Industry: Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices" (June 12, 2008. Docket No. FDA–2008–D–0339). We applaud the Agency's effort to provide

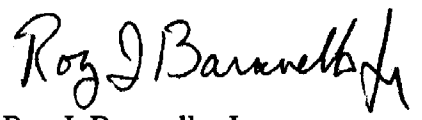

FedEx US Airbill
Express
8630 2184 5712
1 From This portion can be removed for Recipient's records.
Date 8/11/08
FedEx Tracking Number 863021845712
Sender's Name ROY BARANELLO
Phone 484/865-37
Company WYETH
Address 500 ARCOLA RD
City COLLEGEVILLE
State PA
ZIP 19426-39
2 Your Internal Billing Reference 101312
3 To
Recipient's Name
Company
Address
City
State
ZIP
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
RECIPIENT: PEEL HERE
fedex.com 1.800.GoFedEx 1.800.463.3339
8630 2184 5712
Recipient's Copy
FedEx
TRK# 0215 8630 2184 5712
TUE - 12 AUG A2
STANDARD OVERNIGHT
ZD OBTA
20852
MD-US
IAD
Emp# 171727 11AUG08 PMEA
Does this shipment contain dangerous goods?
One box must be checked.
No
Yes
Yes
Dry Ice
Cargo Aircraft Only
7 Payment Bill to:
Sender
Recipient
Third Party
Credit Card
Cash/Check
Total Packages
Total Weight
Credit Card Auth.
Direct Signature
Indirect Signature
519
THIS PACKAGE HAS BEEN X-RAYED
RT 0
FZ 0
5712
08.12

Wyeth

Similarly, we recommend that the sections of the guidance (e.g., IV.B.2. and IV. C.) be revised to reflect this comment as well as the comments provided in I.B. and II.B.,

We are submitting the above comments in duplicate. Wyeth appreciates the opportunity to comment on the above-mentioned proposed study and trusts that the Agency will take these comments into consideration.

Sincerely,



Roy J. Baranello, Jr.
Assistant Vice President
Regulatory Policy and Intelligence
Global Regulatory Affairs

Wyeth

provided in the regulations or guidance, we are unclear what type of information FDA is expecting to support a labeling change that differs from an FDA recognized standard or to justify why a change is not needed.

We recommend that the guidance (Sections IV.B.2. and IV.C.) be revised for clarity to include specific examples of the type of information (e.g., type of analysis, scientific justification) that FDA would expect to support a labeling change that differs from a standard recognized by FDA or to justify why the applicant believes no change in the label is needed. 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.

INFO. COLLECTION

D. Timing for Application Holder to Respond

Section IV (lines 166 – 170) of the draft guidance recommends that the application holder, no later than 60 days after the publication of the FR notice, submit updated labeling or provide a written explanation why they believe the standard is not applicable to its antibacterial product. In addition to our comments in I.B. and II.B., we believe that the 60 days does not provide an adequate time period for the application holder to assess the revisions to the standard, review the drug product labeling including clinical and microbiological efficacy, microbiology data, etc. In specific instances, data may need to be generated for the application holder to justify why a labeling change may/may not be needed and in many instances this will likely require longer than 60 days.

Consistent with our recommendations in I.B. and II.B., we recommend that the guidance be revised to remove the "not later than 60 days" timeframe for the application holder to respond after the publication of the Federal Register notice. We recommend that the guidance be revised to recommend submission of a letter of intent to amend the labeling following a request by the by the FDA to revise labeling, as recommended in our comments in II.B.

Specifically, we recommend that lines 167-170 be revised from, "Not later than 60 days after FDA publicly recognizes a standard that is relevant to the application holder's product, the application holder should submit updated labeling ... or provide a written explanation why it believes the standard is not applicable to its antibacterial drug product ... to "~~Not later than 60 days after~~ Once FDA notifies the application holder of a FDA recognized standard, the application holder should submit ~~updated labeling~~ a letter of intent to amend the labeling, as appropriate... ~~or provide a written explanation why it believes the standard is not applicable to its antibacterial drug product....~~"

Wyeth

We recommend that the guidance include information describing FDA's approach and scientific methodology (i.e., in support of "scientific judgment") to accept or reject a standard (also refer to II. B. below). Additionally, we recommend that FDA include in its evaluation and decision making any additional information that may be available from the application holder.

B. FDA Communication to the Application Holder – Recognition of a Standard

As per the draft guidance (lines 140-143, 250-258), FDA intends to recognize susceptibility test criteria, and associated test methods and quality control parameters, by publishing annually in the Federal Register (FR). Additionally, as per line 166, "When FDA recognizes a standard that is different from the information in the *Microbiology* subsection of the labeling for the application holder's product, the difference should be specifically evaluated by the applicant (§ 201.56(a)(2))." Wyeth is concerned that the FDA does not intend to communicate directly with the application holder regarding the outcome of FDA's scientific review, the rationale for accepting/rejecting a standard (refer to II.A.), or specific labeling changes requested. 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.

Wyeth recommends that FDA provide a written communication directly to the application holder and include the FDA's scientific assessment, its rationale for acceptance of a standard, and a specific request for a revision of labeling if deemed appropriate. We also recommend that line 166 be revised from "the difference should be specifically evaluated by the applicant...." to "the difference should be specifically evaluated by the applicant <u>following notification by the FDA</u>."

C. Updating Susceptibility Test Information in the Labeling - Supporting Data

Section IV. B.2. of the draft guidance "Approaches to Updating Labeling-Updating Through Submission of Information that Supports Labeling Different from a Standard Recognized by FDA" states (lines 207-210), "The applicant should submit ... any proposed change ...along with the information that supports a change...." Similarly, Section IV.C. states (lines 226-229) "If the Applicant Believes No Change to the Labeling is Needed", "...the applicant should provide written justification to the FDA not later than 60 days...." Since the recommendations provided in the draft guidance have not been previously

Wyeth

labeling, provide written submissions to FDA justifying a decision to update their labeling in a manner different from that proposed by a third party standards development organization, or provide written submissions to FDA in cases where the application holder decides that a labeling update is not needed. Thus, the draft guidance would, if finalized, establish several new, burdensome regulatory requirements that add to the existing requirements of 21 C.F.R. 201.56(a)(2). Under rulemaking procedures, FDA would, among other things, be required to consider the impact of its proposed rule on industry, evaluate whether the benefits of the proposed rule would outweigh those burdens, and publish the results of that evaluation in the preamble to the proposed rule.

FDAAA section 1111 authorizes FDA to identify and periodically update "clinically susceptible concentrations" and make those findings publicly available. FDAAA does not, in this case, specifically authorize FDA to require labeling changes based on this information[2]. As such, we believe that FDA should describe how it will "identify" such concentrations as well as the circumstances under which FDA might consider a manufacturer's labeling to be false or misleading under 21 C.F.R. 201.56(a)(2). However, we do not believe that this guidance should be used to establish specific reporting requirements, time frames, or labeling changes, and that the need for these additional requirements should be evaluated through a formal rulemaking process.

We 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[3]. The guidance should not, however, impose new regulatory requirements (i.e., timeline to respond, need to provide written justification if not accepting a standard or accepting a different standard) that go beyond those currently defined in 21 C.F.R. 201.56(a)(2). Furthermore, we recommend that any new proposed requirements regarding timing and providing written justifications be published for public comment via the formal rulemaking process.

II. SPECIFIC COMMENTS

A. Criteria for Acceptance of a Standard

The draft guidance (lines 147-148) acknowledges FDA's authority "...to accept or reject for recognition (based on FDA's scientific judgement) any susceptibility test interpretive criteria...." However, it is unclear what criteria FDA would employ to accept or reject one standard in favor of another. We believe this information is critical to the evaluation of the FDA recognized standard by the application holder

[2] Other provisions in FDAAA do authorize mandatory labeling changes in certain circumstances.
[3] For example, clearly stating the purpose of the labeling supplement, not combining the labeling changes with any other CBE or Prior Approval labeling revisions being submitted.

Wyeth

development organization for a specific bacterium treated by a specific approved antibacterial product."

Wyeth is concerned that FDA's proposed approach is, in effect, utilizing the standards development organizations to provide scientific advice in a capacity that is similar to the role of FDA advisory committees. However, the standards development organizations are not subject to the provisions Congress enacted to ensure that the advisory committee process is transparent, open, and free from improper influence[1]. FDA has previously acknowledged the need to identify potential conflicts of interest of Advisory Committee members and has mostly recently reiterated its importance as indicated by press release of August 4, 2008, "Improved Policies Regarding Transparency, Public Disclosure for Advisory Committees." Currently, the standards development organizations are not subject to these types of requirements. As such, the FDA as well as those utilizing these standards may not benefit from the transparency of potential conflicts of interest in organizations that serve in an FDA advisory capacity.

Because we believe that FDA is proposing that standard development organizations serve in an FDA advisory capacity, Wyeth recommends that such organizations be subject to procedures similar to those used for FDA's Advisory Committee's for disclosure of potential conflicts of interest of its members and that FDA evaluate these potential conflicts of interests in its assessment to accept or reject standards from these organizations.

B. Recommendations Perceived as Obligations via Guidance

FDA's draft guidance appears to impose several new obligations on drug manufacturers, which we believe should be subject to rulemaking requirements. While the guidance states that it is non-binding and an alternate approach may be used, the specificity of the directions for manufacturers and their interrelationship with 21 C.F.R. 201.56(a)(2), make clear that application holders would be expected to: (1) update their labels in accordance with FDA-recognized standards within 60 days of the *Federal Register* notice; (2) update their labels without relying on the standards, so long as they provide additional data to support the label change, within 60 days of the *Federal Register* notice; or (3) provide written justification to FDA within 60 days of the *Federal Register* notice if the holders believe that no label change is necessary. We believe these requirements go beyond FDA's current regulation at 21 C.F.R. 201.56(a)(2), which obligates application holders to update their labels when new safety information becomes available that renders the previously-approved labeling inaccurate, false, or misleading.

Additionally, the current regulation does not, as this guidance would, establish specific time frames in which application holders would be required to: update their

[1] The Federal Advisory Committee Act (5 U.S.C. App.) requires that all advisory committee meetings and records be open to the public, permitting adequate opportunity for participation and review.

Wyeth Pharmaceuticals Inc.
P.O. Box 8299
Philadelphia, PA 19101-8299

Wyeth

August 11, 2008

0235 8 AUG 12 A10:57

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

RE: Docket No. 2008D–0339, June 12, 2008 (73 FR, 33438 - 33440)

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments on the FDA draft Guidance For Industry entitled "Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices."

Wyeth is one of the largest research based pharmaceutical and healthcare products companies and is a leading developer, manufacturer, and marketer of prescription drugs, biopharmaceuticals, vaccines, and over the counter medications. Wyeth appreciates the opportunity to comment on the above-mentioned Federal Register notice; our comments are provided below.

I. GENERAL COMMENTS

A. Use of Standards Development Organizations

Section 1111 of the FDA Amendments Act (FDAAA) requires FDA to "identify (where such information is reasonably available) and periodically update clinically susceptible concentrations" and to "make such clinically susceptible concentrations publicly available, such as by posting on the Internet, not later than 30 days after the date of identification and any update under this section." In the draft guidance (lines 140-143), FDA indicates that it intends to satisfy this requirement by recognizing standards developed by one or more nationally or internationally recognized standard development organizations and publishing an annual list of such standards in the *Federal Register*. FDA asserts that this approach is "consistent with FDA's current authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360d(c)) to recognize a standard for [medical] devices by issuing a *Federal Register* notice."

However, unlike devices, Congress has not explicitly granted FDA the authority to rely on third party consensus standards for drugs. Recognizing this difference FDA notes (lines 147-150) that it will retain control over the recognized standards, stating: "FDA retains the authority to accept or reject for recognition (based on our scientific judgment) any susceptibility test interpretative criteria, or associated susceptibility test method or quality control parameters, developed by a standard

FDA-2008-D-0339 C

Draft Guidance for Industry Updating Labeling for Susceptibility Test Information in systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices		
Section	**Page or Line Number**	**Comment or proposed replacement text**
	149	parameters, developed by a standards development..."
Section III	Page 4/Line 154	Reference should be to Section "IV.F" not "III.F".
Section IV	Lines 166, 192, 206, 228	Will the FDA notify the application holder of any planned changes to their drug prior to making those changes public? When does FDA anticipate the annual *Federal Register* notice will be published each year (e.g. first quarter, second quarter, third quarter or fourth quarter)?
Section IV	Page 6/ Line 167	A 90-day period would be helpful rather than a 60-day period.
Section IV "D"	Page 6/ Line 236	Suggested edit for Heading: "Addressing the Status of the *Microbiology* Subsection in the NDA/ANDA Annual Report"
Section IV "D"	Page 6/ Line 238	Suggested edit: "Application holders should also include in their NDA/ANDA annual report an assessment of whether the information in the *Microbiology* subsection of their product labelling is current or changes are needed (21 CFR 314.81(b)(2)(i)).
		Please clarify if prior approval supplements already approved and/or prior approval supplement under review should be identified in the NDA/ANDA annual report.
Section IV "D"	Page 6/ Line 239	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, PD data, etc. and level of detailed information generated inside and outside the US.
Section IV "F"	Page 7/ Line 251	Suggested edit: "...identification ~~and~~ of any update. As described in section ~~II.C~~ III..."
Section V	Page 7/ Lines 273 - 279	Software updates for AST devices sometimes take an extended period to implement: consultation on ways to best facilitate the timing of this sometimes complex process is suggested.

[Docket No. 2008-D-0339]

Draft Guidance for Industry Updating Labeling for Susceptibility Test Information in systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

General Comments

This is an excellent approach and we look forward to seeing it implemented.

Draft Guidance for Industry Updating Labeling for Susceptibility Test Information in systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices		
Section	**Page or Line Number**	**Comment or proposed replacement text**
Background "A"	Page 3/ Line 48	Following the lead of the FDAAA wording, the guidance appears focused entirely on antibacterial testing. However, and as recognized by CLSI document M23, interpretation of antifungal susceptibility testing follows essentially identical patterns and could be handled using the same procedures. Specifically, Paragraph 1.1 of M23-A3 states: "Although differences may arise because of fungus-related limitations (e.g., clinical data may be more limited than for bacteria, numbers of isolates available for testing may be limited for some relevant genera or species), the process of determination of interpretive breakpoints and QC for fungi is broadly the same as for the bacteria. Unless otherwise specifically noted herein and making due allowance for our still evolving understanding of relevant differences for fungi, it may thus be assumed that the principles described in this document apply equally to antifungal agents." Following this logic, it would be helpful if either this document included antifungal testing or if a parallel document for antifungals were made available. If the document is going to stay focused entirely on antibacterial, some of the wording (e.g., line 58) could be made more specific to bacteria.
Background "B"	Page 3/ Line 95	Suggested edit "Additional data on susceptibility of bacteria and response to therapy may show an altered relationship over time between those two parameters for a particular bacterial species to a particular antibacterial drug."
Background "B"	Page 3/ Line 99	Suggested edit "~~Changes in~~ Decreased susceptibility may raise efficacy or safety concerns when out of date interpretative breakpoint criteria are ~~susceptibility test~~ used in guiding treatment of patients with the indicated infection(s)."
Background "B"	Page 3/ Line 102	Suggested edit "~~Microbiological methods~~ Antimicrobial MIC dilution and agar disk diffusion methods and their respective quality control standards may be refined to improve performance or better assess the quality control of susceptibility testing."
Section III	Page 4/ Line	Suggested edit "...susceptibility test method or quality control

AstraZeneca

August 5, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number FDA-2008-D-0339
Response to FDA Call for Comments
Draft Guidance for Industry Updating Labeling for Susceptibility Test Information in systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

Dear Sir or Madam:

Reference is made to the June 12, 2008 Federal Register notice announcing the request for comments on "Draft Guidance for Industry Updating Labeling for Susceptibility Test Information in systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices."

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Cindy M. Lancaster, US Executive Director, Regulatory Affairs, at (302) 885-1348.

Sincerely,

Darci L. Bertelsen / DT

Darci L. Bertelsen,
Regulatory Affairs Director,
Telephone: (302) 886-7355
Fax: (302) 886-2822

DLB

Enclosure

Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Hospira

Comment:

The above referenced sections within the draft guidance state when susceptibility labeling changes are needed, a supplement to the application is to be made not later than 60 days after the publication of the *Federal Register* notice. Hospira thinks that the amount of time given to assess, possibly test, and incorporate susceptibility updates in the labeling is not reasonable. 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, especially if supporting data is required to justify Approach IV.B.2. If the applicant is required to revise the labeling for either approach, the internal revision process including review, proofing and studio time can again well exceed the 60 days suggested. Therefore, based on the time required for assessment and revisions, Hospira suggests that the Guidance Document be revised to allow for a supplement to the application be submitted not later than 120 days after the publication of the *Federal Register* notice.

INFORMATION COLLECTION

Hospira

COMMENTARY
Docket No. FDA-2008-D-0339
Draft Guidance for Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices

Please refer to:

IV. UPDATING SUSCEPTIBILITY TEST INFORMATION IN ANTIBACTERIAL DRUG PRODUCT LABELING

A. Periodic Evaluation of Information in the *Microbiology* Subsection (Lines166-170)

Not later than 60 days after FDA publicly recognizes a standard that is relevant to the application holder's product, the application holder should submit updated labeling (see section III.B) or provide a written explanation why it believes the standard is not applicable to its antibacterial drug product (see section III.C).

B. Approaches to Updating the Labeling

1. *Updating Through Reliance on a Standard Recognized by the FDA* (Lines 191-193)

The applicant should submit a prior approval labeling supplement containing the appropriate changes not later than 60 days after the publication of the *Federal Register* notice.

2. *Updating Through Submission of Information that Supports Labeling Different rom a Standard Recognized by FDA* (Lines 204-207)

Application holders who wish to update their product's labeling with susceptibility test information that differs from the standards that the FDA recognizes in the *Federal Register* should submit proposed labeling as a supplement to their application, not later than 60 days after the publication of the *Federal Register* notice.

CUBIST

Conclusion.

We appreciate your consideration of these comments and look forward to continuing our dialogue with the Agency. If you have any questions or concerns, please contact me at any time at (202) 347-3278.

Sincerely,

/s/

Mark T. Battaglini, Esq.
Vice President, Government Affairs
Cubist Pharmaceuticals

601 Thirteenth Street, NW
Suite 580 - South
Washington, DC 20005