Norden, Janet M

Subject:	Updated: Internal discussion on NDA 22-059, Tykerb (lapatinib)
Location:	CDER ONDIO Instant Meeting; CDER WO 6305 conf rm Bldg22
Start:	Thu 8/2/2007 12:00 PM
End:	Thu 8/2/2007 1:00 PM
Show Time As:	Tentative
Recurrence:	(none)
Meeting Status:	Tentatively accepted
Required Attendees:	CDER SEALD Labeling; Burke, Laurie B; Axelrad, Jane A; Bernstein, Michael; Peat, Raquel; Rosario, Lilliam; Pierce, William (CDER); Colangelo, Kim M; Sadove, Elizabeth; Jenkins, John K; Kweder, Sandra L; Jones, Glen D (CDER); Ibrahim, Amna; Ray, Seth; Loewke, Sally A; Norden, Janet M
Optional Attendees:	Weiss, Karen; Pazdur, Richard; Justice, Robert
Importance:	High

This is an internal meeting to discuss GSK's proposal to submit revisions to approved Tykerb (lapatinib) labeling to include an additional adverse reactions (interstitial lung disease and pneumonitis). This change would be inserted into the 'Warnings and Precautions' section of labeling. Before PLR, this form of revision to the labeling would be submitted as a Change Being Effected (CBE) to the NDA because the change would strengthen the 'Warnings and Precautions' and lead to increased safe use of the drug. Based on the Rule, this form of change impacts the "Highlights" section hence we can no longer submit such a change as a CBE but rather as a PAS. This meeting is to discuss this policy.

For those that can not attend in person, the call in # is [redacted], pass code [redacted].

Background email:

FW: Summary of issue regarding...

An agenda will be sent as we approach the meeting.
POC: LT Peat, 301-796-0700

Norden, Janet M

From: Colangelo, Kim M
Sent: Tuesday, June 12, 2007 4:19 PM
To: Peat, Raquel
Subject: FW: Summary of issue regarding timely safety updates to prescription drug labeling in PLR format

Attachments: FW: Response to your CBE labeling question; Response to your CBE labeling question; Re: Summary of issue regarding timely safety updates to prescription drug labeling in PLR format

Background for Friday

From: Jenkins, John K
Sent: Tuesday, May 29, 2007 1:01 PM
To: Axelrad, Jane A; Sadove, Elizabeth; Kweder, Sandra L; Colangelo, Kim M
Cc: Bernstein, Michael; Norden, Janet M; Jenkins, John K
Subject: FW: Summary of issue regarding timely safety updates to prescription drug labeling in PLR format

Jane

I know you have been buried in the past few weeks with the legislation and other high priority issues. I need to bring this issue back to toward the top of the inbox since we now have a specific case where a sponsor is asking how they should handle adding an adverse event to a drug label that should also be added to the highlights section. The sponsor would normally do this as a CBE, but are asking for guidance on how to proceed given the PLR. Attached is the text of their message and below is the complete background on this issue.

John

[mailto:[redacted]] From: [redacted]
Sent: Tuesday, May 22, 2007 2:29 PM
To: Robertson, Kim
Subject: NDA 22-059

Dear Kim:

As I mentioned on the telephone, GSK is planning to revise approved Tykerb (lapatinib) labeling to include an additional adverse event (interstitial lung disease and pneumonitis). This change would be inserted into the Warnings and Precautions section of labeling.

Normally, we would revise the labeling and submit it to the NDA as a Change Being Effected (CBE) because the change would strengthen the warnings/precautions and lead to increased safe use of the drug.

But I have been advised by my colleagues that with the new labeling format (specifically the "Hightlights" section), we can no longer submit such a change as a CBE if it impacts the "Highlights" section.

Can you discuss this matter with the medical reviewers at FDA and let us know if this type of change to labeling can be submitted as a CBE?

Thanks and Regards,

rich

Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

John K. Jenkins, M.D.
Director, Office of New Drugs
10903 New Hampshire Avenue
Bldg #22, Room 6304
Silver Spring, MD 20993
301-796-0700
301-796-9856 (fax)
NOTE, New E-mail Address: john.jenkins@fda.hhs.gov

From: Jenkins, John K
Sent: Wednesday, April 25, 2007 8:58 AM
To: Axelrad, Jane A; Sadove, Elizabeth; Kweder, Sandra L; Colangelo, Kim M
Cc: Bernstein, Michael; Norden, Janet M; Jenkins, John K
Subject: RE: Summary of issue regarding timely safety updates to prescription drug labeling in PLR format

Jane

Here are two examples, one recent and one a couple of years old where important safety information was added via a CBE and FDA needed much more time to review the underlying data to make a decision on the approved labeling. Another theoretical example would have been Vioxx. When we met with Merck in September 2004 they had preliminary results of the APPROVe trial that showed an increased risk of CV events. Has Merck not decided to voluntarily withdraw the product it would have been necessary for them to make labeling changes to add warnings about the new findings. We probably would not have issued an approval letter on the labeling changes since we would not have had access to the full study report for review so we could evaluate the actual data that would be added to the labeling. So, we probably would have agreed to interim labeling and asked Merck to submit it as a CBE and we would have made more official determinations later after we reviewed the full study report. The two attached examples, one in OAP and one DRUP are similar in that they led to addition of interim new important safety information the labeling, but without explicit FDA approval. In the DRUP case we later agreed to the labeling with minor revisions and in the OAP example we have not yet completed our review of the data from the new trial. While these two real world examples and the Vioxx hypothetical are related to new safety information from controlled trials, it is also possible that similar scenarios could arise from AERS reports where we want to do a more comprehensive analysis and allow the sponsor to add changes via CBE in advance. It is important to note that the CBE pathway does not mean we do not see and comment on the labeling before it is implemented. In many cases we do work with sponsors on the interim labeling to be added via CBE, but we do not approve it since our review is not yet complete. This is an important pathway to allow important new safety information to get to the labeling in a timely manner, and it is even more important today given our transmittal of new labeling to the NLM where it can be made available much more rapidly to prescribers and third party vendors. This is why most of our objected to the no CBE changes to the Highlights section of PLR and why we think it is important that we find a way to waive that requirement in appropriate cases.


FW: Response to your CBE label...


Response to your CBE labeling ...


Re: Summary of issue regarding...

John

John K. Jenkins, M.D.
Director, Office of New Drugs
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301-796-9856 (fax)
NOTE, New E-mail Address: john.jenkins@fda.hhs.gov

From: Axelrad, Jane A
Sent: Monday, April 23, 2007 4:50 PM

July 25, 2007

GlaxoSmithKline

GlaxoSmithKline
2301 Renaissance Boulevard
P.O. Box 61540
King of Prussia, PA
19406-2772

Tel. 610 787 7000
Fax. 610 787 7777
www.gsk.com

Robert Justice, M.D., Director
Division of Drug Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
N/A
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 022059/0002; TYKERB® (lapatinib ditosylate)Tablets
Supplement: Prior Approval, Labeling (Interstitial Lung Disease and Pneumonitis)

Dear Dr. Justice:

Reference is made to our approved NDA 22-059 for Tykerb® (lapatinib) tablets. GlaxoSmithKline (GSK) has determined that sufficient evidence exists for the company to add interstitial lung disease and pneumonitis to the WARNINGS/PRECAUTIONS and ADVERSE REACTIONS section of *Tykerb* labeling.

These changes are designed to strengthen the safe use of the drug and would normally be made as Changes Being Effected under 21 CFR 314.70(c)(6)(iii)(A). However, because these changes affect the Highlights section of labeling 21CFR201.57(a), the proposed changes require FDA approval prior to distribution of the product made using the change under 21CFR314.70(b). We are requesting expedited review of this supplement (3 days) as described below.

Justification for the labeling changes is presented in Attachment.

We are submitting the final printed labeling electronically in accordance with the *Guidance for Industry, Providing Regulatory Submissions in Electronic Format – NDAs, January 1999*. Please see the Guide to FDA Reviewers for detailed information about this electronic submission. Microsoft Word versions of the revised labeling showing all changes on the current version and a clean copy with all changes accepted are provided as reviewers' aids. The content of the labeling is also being submitted in SPL format in accordance with the *Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Content of Labeling, April 2005.*

Normally, for a CBE labeling supplement for safety information, the revised labeling would be implemented on the GlaxoSmithKline Corporate website within three (3) days

after submission. As the Highlights section of the labeling is also revised, the regulations cited above require a prior approval supplement. Mr. Robert Watson conferred with Dr. Robert Justice on 19 July 2007 regarding such a change to final approved labeling for *Tykerb,* and it was agreed the Division should reviewed the supplement promptly.

If you have any questions, please call me at (610) 787-3724; I can be reached by fax at (610) 787-7062.

Sincerely,

Richard Swenson, Ph.D.
Senior Director
Regulatory Affairs

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

Saville, Rebecca

From:	Burke, Laurie B
Sent:	Thursday, January 03, 2008 5:07 PM
To:	Roeder, David L
Cc:	Saville, Rebecca
Subject:	RE: Levaquin CBE-0 converted to PA supplements

This is a good one! Thanks to you both.

Laurie

-----Original Message-----
From: Roeder, David L
Sent: Thursday, January 03, 2008 4:56 PM
To: Burke, Laurie B
Cc: Saville, Rebecca; Roeder, David L
Subject: FW: Levaquin CBE-0 converted to PA supplements

Hi Laurie,
Rebecca Saville (DSPRP) provided the attached example for John regarding the need to allow CBEs that change the Highlights section. I think it's a pretty good one.
Dave

-----Original Message-----
From: Saville, Rebecca
Sent: Thursday, January 03, 2008 4:48 PM
To: Roeder, David L
Subject: Levaquin CBE-0 converted to PA supplements

Hi Dave,

In June 2007, DSPTP approved class labeling to standardize the language pertaining to hepatotoxicity associated with the use of fluoroquinolones. J&J, the sponsor of Levaquin, complied, but apparently investigated the incidence of hepatotoxicity with the use of Levaquin and in the current supplements below, want to further strengthen the hepatotoxicity language in the Levaquin labeling. These labeling supplements include an analysis of reports of hepatotoxicity and propose strengthening the Warnings and Precautions section and patient counseling section. J&J appropriately submitted them as CBE-0 supplements in November 2007. Because the Recent Major Changes and W&P subsections of the HIGHLIGHTS section need to also be changed, and thus only reviewed as prior approval supplements per PLR regulations, we notified J&J and converted the CBE-0 supplements to PA supplements because we needed time to review and approve them. Fortunately, J&J had not yet circulated FPL and the changes have not been included in packaging; however, J&J has expressed concern about the delay in reporting. We are trying to finish the review by the end of the month.

Thanks,
Rebecca

-----Original Message-----
From: cderdocadmin@cder.fda.gov [mailto:cderdocadmin@cder.fda.gov]

Sent: Wednesday, December 19, 2007 4:14 PM
To: Saville, Rebecca; Willard, Diana M
Subject: DFS Email - N 021721 SLR 019 09-Nov-2007 - Supplement Letters

Document room update the following:

		Decision Date	Decision Code
N 021721 SLR 019	09-Nov-2007	19-Dec-2007	:
N 020635 SLR 055	09-Nov-2007	19-Dec-2007	:
N 020634 SLR 051	09-Nov-2007	19-Dec-2007	:

Mail paper copy to

DISTRICT OFFICE

Document Type: Supplement Letters
Letter Group: Acknowledgement Letters
Letter Name: Prior approval supplement acknowledgment letter
Submission Description: 121907HpttxPAackLtr

Author(s)/Discipline(s)

1. Rebecca Saville, CSO

Signer(s)

1. Rebecca Saville
   19-Dec-2007
2. Rebecca Saville
   19-Dec-2007

Supervisory Signer(s)

1. Rebecca Saville
   19-Dec-2007

Saville, Rebecca

From: Saville, Rebecca
Sent: Tuesday, January 08, 2008 7:51 AM
To: Albrecht, Renata; Jenkins, John K
Cc: Kweder, Sandra L; Colangelo, Kim M; Chazin, Howard; Burke, Laurie B; Cox, Edward M; Miller, Kristen; Willard, Diana M; Roeder, David L
Subject: RE: Levaquin (levofloxacin) Hepatotoxicity labeling supplements

Attachments: RE: Levaquin CBE-0 converted to PA supplements; 090014698019c1bc.pdf


RE: Levaquin CBE-0 converted t...


090014698019c1bc .pdf (25 KB)

Hi,

The medical officer is reviewing the current PA SLR for hepatotoxicity and hopes to be done his review by the end of this month.

We have had 5 labeling changes to the Levaquin PI since the FQ class labeling for hepatotoxicity in June was approved. These were as follows:

911/07 - SE5 addition of pediatric safety information
9/14/07 - SE2 addition of a short course 750 mg qd treatment of cUTI and AP
11/15/07 - SLR addition of geriatric information that was missed during the cUTI applications
11/16/07 - CBE that corrected administration directions for the oral solution
12/13/07 - CBE that addressed FQ class labeling regarding phototoxicity.

We also had a OND managed chemistry CBE (stability of the IV after removal of the container overwrap) due in December, but we issued an approvable letter for these applications.

Because all these labeling changes were pending, J&J has not yet started distributing the currently approved PLR in packaging. The hepatotoxicity supplements were submitted in November as CBE-0s, and J&J was running low on the old PI in FPL format for product packaging; thus, they were asking us how to make changes to the Highlights section to add the hepatotoxicity CBE-0 information and start using the newly approved PLR. We then converted the CBE-0s to PA SLRs in order to review them, and thus, J&J can now use the PLR approved on December 13, 2007 as the PI in packaging/distribution. The unapproved proposed hepatotoxicity information has not been included (as a CBE-0) in the PLR included in product packaging/distribution, but has been distributed with promotional materials to physicians.

I hope all this helps. Let me know if you have more questions.

Regards,
Rebecca

From: Albrecht, Renata
Sent: Monday, January 07, 2008 4:41 PM
To: Jenkins, John K
Cc: Kweder, Sandra L; Colangelo, Kim M; Chazin, Howard; Burke, Laurie B; Cox, Edward M;

Saville, Rebecca; Miller, Kristen; Willard, Diana M; Roeder, David L
Subject: Levaquin (levofloxacin) Hepatotoxicity labeling supplements

Hi John,
we send an acknowledgement letter to J&J and included the following paragraph regarding PLR

These supplemental applications, submitted as "Changes Being Effected" (CBE-0) supplements, propose revising information pertaining to hepatotoxicity throughout the labeling for the package insert of Levaquin. Changes of this kind cannot be put into effect according to Physician Labeling Rule regulations that state that the HIGHLIGHTS section of the package insert cannot be modified prior to approval of the supplements. Approved supplements are required for this proposed change prior to distributing drug products made with this change.

The supplement(s) are now PAS, the change has not been implemented, but the SLR is under review.

As far as the changes implemented in 11/07; they are either (a) the new dosage regimen for complicated urinary tract infection or (b) revision in the phototoxicity information or (c) update on pediatric safety data. We've had a number of actions updating the levofloxacin labeling recently.

Also, I understand Rebecca Saville has already provided a summary of the HEPATOTOXICITY supplements to Laurie Burke, so this is the same case.
thanks
Renata

From: Jenkins, John K
Sent: Monday, January 07, 2008 3:16 PM
To: Albrecht, Renata
Cc: Kweder, Sandra L; Colangelo, Kim M; Chazin, Howard; Burke, Laurie B; Cox, Edward M; Saville, Rebecca; Miller, Kristen; Willard, Diana M
Subject: RE: PLR Highlights CBE Waiver

Renata

So, what is the status of this supplement? Did we tell them it had to be PAS or did they go ahead an implement the change including the change to highlights? The labeling that is on Daily Med in in PLR format but does not include the hepatotoxicity changes in either the Highlights or Warnings and Precautions section, but has a revision data of 11/07, so that is a bit confusing to me.

John

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NOTE, New E-mail Address: john.jenkins@fda.hhs.gov

From: Albrecht, Renata
Sent: Sunday, January 06, 2008 12:34 PM
To: Jenkins, John K
Cc: Kweder, Sandra L; Colangelo, Kim M; Chazin, Howard; Burke, Laurie B; Cox, Edward M; Saville, Rebecca; Miller, Kristen; Willard, Diana M
Subject: RE: PLR Highlights CBE Waiver

John,

The drug is Levaquin (levofloxacin) by J&JPRD, and the adverse event is Hepatitis. The cover letter is attached; these CBE-SLRs were submitted November 9, 2007.

For some reason, I don't see the submission to NDA 20-634/S051 in the Electronic Document Room (it's item 28 on our pending SLR list).

I did find the "cross-referenced" submissions in the EDR (links below).
\\CDSESUB1\NONECTD\N20635\S_055\2007-11-09
\\CDSESUB1\N21721\S_019\2007-11-09

The project manager for Levaquin is Rebecca Saville.
Please let me know if additional information is needed.
thanks for taking on this test case.
Renata

From: Jenkins, John K
Sent: Wednesday, January 02, 2008 11:24 AM
To: Albrecht, Renata
Cc: Kweder, Sandra L; Colangelo, Kim M; Chazin, Howard; Burke, Laurie B; Cox, Edward M
Subject: PLR Highlights CBE Waiver

Renata

Do you still have the safety issue.pending that you mentioned to me in the hallway a couple of weeks ago for a safety issue where the sponsor wants to submit a CBE but is blocked by the PLR provision that says no changes to Highlights via CBE? If so, please let me know more of the specifics. We have been getting movement from OCC on our request for a waiver authority in such cases and your's might be our "test case' to push this forward.

John

Laurie: Are you aware of any other good "test cases" we might want to pursue?

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10903 New Hampshire Avenue

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NOTE, New E-mail Address: john.jenkins@fda.hhs.gov

Saville, Rebecca

From: Willard, Diana M
Sent: Friday, February 08, 2008 1:40 PM
To: Saville, Rebecca
Subject: FW: PAS waiver for CBE changes to HL: Levaquin

Importance: High

Attachments: Levaquin Hepatotox CBE waiver 2-6-08.doc

Levaquin patotox CBE waiver

A few minor edits - see if they help it read better and if not, I'm OK with what you wrote. I think it makes the FDA look bad to issue 3 ACK letters!

Will Renata now sign the AP letters?

Thanks,
Diana

-----Original Message-----
From: Saville, Rebecca
Sent: Wednesday, February 06, 2008 3:54 PM
To: Willard, Diana M
Cc: Albrecht, Renata; Roeder, David L
Subject: FW: PAS waiver for CBE changes to HL: Levaquin
Importance: High

Hi Diana,

Attached, please find the letter granting a waiver for the Levaquin hepatotox SLRs for your review. Laurie said to use the ack letter template (I called her w/ a few questions for clarification).

Thanks!

From: Burke, Laurie B
Sent: Wednesday, February 06, 2008 2:07 PM
To: Saville, Rebecca
Cc: Colangelo, Kim M; Thompson, Elizabeth; Delasko, Jeanne; Furness, Melissa; CDER SEALD Labeling; Roeder, David L
Subject: PAS waiver for CBE changes to HL: Levaquin

Rebecca,
Please use the following language in your response concerning the Levaquin hepatotoxicity labeling changes with changes to HL. Please let me know if you have any questions. And please notify CDER SEALD Labeling when the letter has issued so that we can notify those who are interested (e.g., Dr. Jenkins and the Waiver

Committee) and track of this type of action. Thank you!
Laurie

We refer to your supplemental new drug application dated [INSERT DATE], proposing to strengthen the safety information in the Highlights of prescribing information and other parts of the labeling. Because of the importance of the proposed changes in strengthening information regarding safe use of the drug, under 21 CFR 314.90(b), we are waiving the requirement at 21 CFR 314.70(b)(2)(v)(C) for prior approval of changes to Highlights and accepting this as a "Changes Being Effected" supplement. Therefore, these changes may be implemented immediately.

We will inform you whether or not these changes are approved at the conclusion of our review.