Burton, Carolyn

To: Bradshaw, Sheldon
Cc: seth; annw; heidi
Subject: RE: Your Question Regarding Highlights and Changes Via CBE Supplements

I'm waiting to hear back from a CDER staffer who thought the issue might be covered, but I'm not convinced. Rachel Behrman, the lead for CDER, thinks that changes to the Highlights should not be made via CBEs. Unless the staffer comes up with something better, I was going to ask Rachel to vet her position with the rest of CDER management. Is that ok with you? Then we'll have to consider whether there is any way to revise 314.70 as part of this rule ("logical outgrowth" issue).

Seth

-----Original Message-----
From: Bradshaw, Sheldon
Sent: Tuesday, September 20, 2005 7:40 PM
To: Ray, Seth
Subject: Re: Your Question Regarding Highlights and Changes Via CBE Supplements

That is correct (and I agree that the reg should be changed). Let me know what you here back from the center.

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Ray, Seth <seth.ray@cder.fda.gov>
To: Bradshaw, Sheldon <Sheldon.Bradshaw@FDA.GOV>
CC: Ray, Seth <seth.ray@cder.fda.gov>; Wion, Ann <AWion@OC.FDA.GOV>; Gertner (Forster), Heidi <heidi.gertner@fda.gov>
Sent: Tue Sep 20 19:21:32 2005
Subject: RE: Your Question Regarding Highlights and Changes Via CBE Supplements

I've looked through the rule and proposed accompanying guidance document and I don't believe your question is addressed. [The guidance only states that for approved applications that become subject to the rule, and for applicants voluntarily revising older labeling, new labeling would be submitted as a prior approval supplement.] I have an e-mail into CDER to see whether I've overlooked something.

In light of Kallas and the preemption provision contained in the rule, is it your view that all or certain changes to highlights should not be permitted via CBE supplements? We would likely need to amend 314.70(c) in conjunction with the rule.

Seth

-----Original Message-----
From: Bradshaw, Sheldon
Sent: Tuesday, September 20, 2005 6:17 PM
To: Ray, Seth
Subject: Re: Your Question Regarding Highlights and Changes Via CBE Supplements

That is correct.

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Ray, Seth <seth.ray@cder.fda.gov>
To: Bradshaw, Sheldon <Sheldon.Bradshaw@FDA.GOV>

CC: Ray, Seth <seth.ray@cder.fda.gov>
Sent: Tue Sep 20 18:03:59 2005
Subject: Your Question Regarding Highlights and Changes Via CBE Supplements

In your question, you assume that the company and FDA have agreed on new labeling with a highlights section and then the company subsequently wants to add or strengthen a warning in the highlights via a CBE supplement, right?

Seth

Seth Ray
Food & Drug Division, OGC
301-827-7144
sray@oc.fda.gov

Norden, Janet M

From: Temple, Robert
Sent: Wednesday, October 12, 2005 7:11 PM
To: Jenkins, John K; Behrman, Rachel E; Galson, Steven
Cc: Kweder, Sandra L; Oliva, Armando; Norden, Janet M
Subject: RE: Highlights and CBEs

I agree with Rachel. Highlights will be a carefully constructed, terse, critically designed summary of what is most critical. I don't believe we can allow an unreviewed change to be made by a sponsor for what could be a variety of reasons (legal concerns, etc) and that may not be optimally conveyed. If we are in a state of great urgency we have a number of ways to manifest it, including PHAs and the various ways we are developing for putting not yet labeled stuff out. We could also review the labeling change rapidly. If we know the data surely it can be done in a week or a couple days. If we don't know the data do we really want the Highlights changed? I think we're talking here about a matter of just a few days' delay, at most.. Realistically, you always have a few days and the labeling change isn't the most effective way to communicate about a problem anyway. Certainly it does little now but even when the NLM Daily Med is operative it requires that someone go find it. I have similar feelings about a Medguide. It does seem possible, as Rachel suggests, that we could, after a review, specifically PERMIT a CBE change, but I don't see how that saves much time compared to just approving it.

-----Original Message-----
From: Jenkins, John K
Sent: Wednesday, October 12, 2005 3:24 PM
To: Behrman, Rachel E; Galson, Steven
Cc: Temple, Robert; Kweder, Sandra L; Oliva, Armando; Norden, Janet M
Subject: RE: Highlights and CBEs

But your solution invariably involves delay no matter how quickly we try to review the information that supports the change. It seems odd that we will allow a sponsor to add a boxed warning under a CBE (a hypothetical, but real possibility) but not allow them to change the highlights or Medication Guide without our approval no matter how important the safety issue. It just seems at odds with our focus on early notification of safety issues and also I'm surprised OCC does not have concerns about our restricting the sponsor's ability to make timely changes to appropriately warn about new risks with their product. A balance has to be struck between concern about sponsor "bad behavior" and the goals of Daily Med and the Drug Safety Initiatives, which are to get information out quickly. I'll be interested in hearing views from others.

John

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-----Original Message-----
From: Behrman, Rachel E
Sent: Wednesday, October 12, 2005 3:18 PM
To: Jenkins, John K; Galson, Steven
Cc: Temple, Robert; Kweder, Sandra L; Oliva, Armando; Norden, Janet M
Subject: RE: Highlights and CBEs

John-

I think your example actually supports not permitting Highlights to be changed via a CBE. What we really want is coordination and to be informed. We do not want information slipping in and out of Highlights. Once we've seen the information, which typically we have reviewed for an important warning or CI, we can waive the restriction and permit a change via a CBE if we think it's the fastest way to get the information into labeling.

Rachel

-----Original Message-----
From: Jenkins, John K
Sent: Wednesday, October 12, 2005 3:12 PM
To: Behrman, Rachel E; Galson, Steven
Cc: Temple, Robert; Kweder, Sandra L; Oliva, Armando; Jenkins, John K
Subject: RE: Highlights and CBEs

Rachel

The issue of not changing Medication Guides came to light recently and actually pointed out a serious flaw in our rule that says they cannot be changed by CBE. Purdue sent in a CBE for Palladone (hydromorphone) when they got new information about dose dumping when the extended release capsules were taken with alcohol. This dose dumping created a potentially fatal overdose situation. They submitted a CBE to change the labeling and also to add the new increased warnings about use with alcohol to the Medication Guide. It was only later that we were reminded that you cannot change a Medication Guide via a CBE (I guess because the format requires that they say "this information has been approved by FDA"). That said, the information was the type of information that you would want to communicate as rapidly as possible and I think brings into question our policy of not allowing Medication Guides to be changed by CBE. In the Palladone case the drug was not yet marketed, so one could argue they could have waited for our review and approval and then gone to market. But, had the product been marketed already the delay while awaiting FDA approval could have been meaningful, particularly in the age of instant posting of revised labeling on the internet and the potential power for the Daily Med posting to be rapidly disseminated to prescribers and patients. I understand the concerns that a sponsor could change the Medication Guide to note a new safety issue, but do so in a way that underplayed the risk, but we can always require a change later and you could argue that putting the new safety information in quickly, even if followed by a later modification and "upgrade", would be a better outcome than waiting for FDA review and approval. So, I have to say I was somewhat surprised when I learned of the CBE rule on Medication Guides after the Palladone incident. It seemed overly strict, and perhaps that was a reflection of our concern at the time for how sponsors my respond to them and also the fact that they were written at a time when we were in the paper labeling era where there was much less impact on waiting for FDA review and approval. Now in the internet electronic age I wonder if that is the right policy, and whether it is consistent with our stated goal of getting new safety information out to doctors and patients quickly, even in cases where we (FDA) have not fully vetted the information. I think the same argument could be made about the highlights section.

Of note, we took a lot of heat from Congress on the Palladone labeling issue since we did not post the CBE changes on our website since our policy has been to only post approved labeling and we were not willing to approve the Palladone labeling since we were considering the question of whether it should be removed from the market. Senator Grassley criticized the fact that the most recent safety information was not on the FDA website, while it was on the Purdue website. No matter how quickly we might try to review and approve labeling changes there is no way we can keep up with the ability of information to flow quickly in this information age. So, I guess I not only question the idea of not allowing the Highlights to be changed by CBE, but I also question our reg on Medication Guides.

I've copied Armando and Sandy to hear their thoughts. I think the issue warrants further discussion.

John

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-----Original Message-----
From: Behrman, Rachel E
Sent: Wednesday, October 12, 2005 2:02 PM
To: Galson, Steven; Jenkins, John K
Cc: Temple, Robert
Subject: Highlights and CBEs

Steven and John-

Recently, OCC asked us whether Highlights could be changed via a CBE (I don't recall exactly, but

something about a current court case raised this in Sheldon's mind). We realized that the rule is silent on this subject and concluded it would be a mistake to permit a company to change Highlights without our knowledge. We concluded this because of the nature of Highlights. It's a summary and there is going to be considerable judgment in deciding what is included and what is not included. One can easily imagine incentives for including, or excluding, information. In addition, we will need to be very careful about consistency within and between companies, products and classes of products. Finally, the rule goes to great length discussing on FDA will exercise scrupulous oversight over the content of Highlights (including the 1/2 page limit). Moreover, there is precedent - medguides cannot be changed via a CBE. In short, we thought this was an easy call and OCC concurred.

Jane is concerned that I did not involve an appropriately broad group in this decision (I did not elevate this beyond Bob) and, if that is the case, I apologize. If you are uncomfortable with this decision or would like to discuss, please let me know. If you concur with the decision, could you please let Jane know.

Thanks in advance.

Rachel

Locicero, Colleen L

From: Sadove, Elizabeth
Sent: Friday, March 16, 2007 8:31 AM
To: Ray, Seth
Cc: Boocker, Nancy; Norden, Janet M; Colangelo, Kim M; Behrman, Rachel E; Bradshaw, Sheldon; Axelrad, Jane A; Bernstein, Michael
Subject: RE: Waivers from PAS for Highlights

At the time when we crafted these amendments, we discussed that we would permit waivers. This will be a major problem for OND. I will schedule a meeting to discuss. Thanks, Liz

---

From: Ray, Seth
Sent: Thursday, March 15, 2007 5:00 PM
To: Bernstein, Michael; Sadove, Elizabeth
Cc: Boocker, Nancy; Norden, Janet M; Colangelo, Kim M; Behrman, Rachel E; Bradshaw, Sheldon; Ray, Seth
Subject: RE: Waivers from PAS for Highlights

I spoke with Sheldon and OCC does not concur with OND's draft procedure/policy document that would allow sponsors to request a waiver from the review division such that important safety labeling changes to Highlights could be made via CBE supplements. The draft document is inconsistent with the amendments made to 314.70 as part of the PLR. Some of you might not be aware that these amendments were carefully crafted, in response to pending litigation, to ensure that changes to Highlights (other than minor changes) would only be made via prior approval supplements. If CDER managers feel differently, we should meet to discuss. Thanks for bringing this to our attention.

Seth

From: Bernstein, Michael
Sent: Thursday, March 08, 2007 3:41 PM
To: Sadove, Elizabeth; Ray, Seth
Cc: Boocker, Nancy
Subject: RE: Waivers from PAS for Highlights

Seth--

I just wanted to follow up on Liz's request on this. We really need to get a response from you on it and would greatly appreciate if you could take a look at it. Thanks!

Michael

From: Sadove, Elizabeth
Sent: Thursday, March 08, 2007 3:10 PM
To: Ray, Seth
Cc: Bernstein, Michael; Boocker, Nancy
Subject: FW: Waivers from PAS for Highlights

Seth- Please let me know whether you concur with OND's recommended procedures regarding waivers from prior approval supplements for Highlights. I think this is very straight forward and consistent with the discussions that we had when finalizing the PLR requirement.

Kim Colangelo needs a response as soon as possible.
Thanks, Liz Sadove

From: Sadove, Elizabeth
Sent: Monday, February 12, 2007 8:40 AM
To: Ray, Seth
Cc: Bernstein, Michael; Boocker, Nancy
Subject: Waivers from PAS for Highlights

Locicero, Colleen L

From: Axelrad, Jane A
Sent: Thursday, March 29, 2007 6:06 PM
To: Jenkins, John K
Cc: Kweder, Sandra L; Colangelo, Kim M; Sadove, Elizabeth
Subject: RE: Summary of issue regarding timely safety updates to prescription drug labeling in PLR format

Liz is out this week, but I will discuss it with her early next week and get back to you. I have to refresh my recollection of how this was supposed to work and talk to Seth, who is also out this week. Then I'll get back with you with suggestions.

From: Jenkins, John K
Sent: Thursday, March 29, 2007 4:04 PM
To: Axelrad, Jane A
Cc: Jenkins, John K; Kweder, Sandra L; Colangelo, Kim M; Sadove, Elizabeth
Subject: FW: Summary of issue regarding timely safety updates to prescription drug labeling in PLR format

Jane

Liz Sadove may have already made you aware of the issue that Kim documents below. This is not new of course since we had long discussions and specifically objected to this provision in the final PLR. We were over ruled. Now we face the problem of how to get important new safety information into the labeling in a timely manner, which runs up against the PLR requirement for a prior approval supplement. As you can see from Kim's summary below, we developed an approach that would allow us to waive the PAS requirement in appropriate circumstances and we sent that to ORP and OCC for comment. Seth Ray responded that this approach was not acceptable and that the PLR provisions were carefully crafted to address issues related to pre-emption (see attached e-mail string). I'm seeking your advice on where to take this. Requiring a PAS is really at odds with our goal to communicate safety information quickly and this is even more important as we are moving to the era of "real time" electronic labeling at NLM (i.e., the labeling changes can now be an effective rapid communication tool). It is often difficult, if not impossible, for us to specifically agree to the sponsor's proposed changes since we need to review the data, which in some cases can be voluminous and may not be available for some time after the early signal is detected (e.g., report from a new large study stopped by a Data Safety Monitoring Committee). The CBE mechanism provided the flexibility for us to provide some input and comment based on our preliminary review of the data while reserving our final decision on the appropriate labeling language until we completed our review. Help!

John

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

From: Colangelo, Kim M
Sent: Thursday, March 29, 2007 2:05 PM
To: Jenkins, John K; Kweder, Sandra L
Subject: Summary of issue regarding timely safety updates to prescription drug labeling in PLR format

John and Sandy,

As requested during our discussion yesterday, here is a summary of the issue regarding the timely incorporation of important safety information in prescription drug labeling.

With the implementation of SPL and PLR, a centralized committee was established to evaluate waivers for either requirement, and to develop policy and procedures as experience was gained in these areas. The committee was chaired by me, and comprised of the six OND ADRAs, Armando Oliva, Laurie Burke and Lilliam

Rosario from SEALD, and a representative from OGD (Koung Lee). Note: Armando stepped down from the committee a few months after its inception after the larger policy matters were sorted out.

One of the issues raised was not a novel concern: the inability for the sponsor to update product labeling with important new safety information via submission of a "Changes Being Effected" supplement. Under the new labeling rules, important safety changes would require changes to the Highlights, and any change to the Highlights of the label must be submitted for approval before implementation (thereby eliminating the use of CBE supplements for timely incorporation of new safety information.)

The SPL/PLR Waiver Committee developed a procedure (attached) that would allow a sponsor to formally request a waiver of the prior approval requirement and submit the changes as a CBE supplement. This proposal was sent to ORP for opinion and for consult to OCC. The response from OCC (through ORP) is attached, including a separate email from ORP to OCC expressing concerns with their decision.

I have subsequently had a conference call with ORP (Liz Sadove) and OMP (Janet Norden) on this matter and was informed that it would not be likely that a proposal involving the CBE mechanism for changes to Highlights would be found acceptable due to pre-emption concerns with the Highlights. If we wanted to pursue this, they recommended that we consider other mechanisms to get this type of safety information out in an expeditious manner, and to be ready to articulate those options along with strong justification and data to support our proposals. They also stressed that we would need the support of the Center Director to move this forward.

Please let me know if you have any questions, or if I can provide additional background/information on this matter. The SPL/PLR Waiver Committee meets again on April 10 and could begin work on alternative strategies at that time if desired.

Kim

<< File: PAS waiver procedures - clean ORP.doc >> << Message: FW: Waivers from PAS for Highlights >> << Message: RE: Waivers from PAS for Highlights >>

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Locicero, Colleen L

From: Locicero, Colleen L
Sent: Wednesday, April 25, 2007 9:15 AM
To: Norden, Janet M
Subject: RE: Summary of issue regarding timely safety updates to prescription drug labeling in PLR format

Thanks!

From: Norden, Janet M
Sent: Wednesday, April 25, 2007 9:04 AM
To: Locicero, Colleen L
Subject: FW: Summary of issue regarding timely safety updates to prescription drug labeling in PLR format

FYI - JN

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.

John << Message: FW: Response to your CBE labeling question >> << Message: Response to your CBE labeling question >> << Message: Re: Summary of issue regarding timely safety updates to prescription drug labeling in PLR format >>

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