Preemption

Axelrad, Jane A

From: Jenkins, John K
Sent: Thursday, May 22, 2003 5:06 PM
To: Axelrad, Jane A; Jenkins, John K
Subject: Fw: Comments on preemption argument

Jane

Here are some thoughts on the document. I have not addressed the policy question of whether this is a good idea since I'm not sure I know all the issues well enough to make a judgement. I do think the arguments and data in support of the proposed policy are very flawed. I did not finish all possible comments, that could take many more hours or days, but I think the below is a good start.

John K. Jenkins, MD
Director
Office of New Drugs
Center for Drug Evaluation and Research
301-594-5400

Sent from my BlackBerry Wireless Handheld (www.BlackBerry.net)

-----Original Message-----
From: [redacted]
To: jenkinsj@cder.fda.gov [redacted]
Sent: Thu May 22 17:01:19 2003
Subject: Comments on preemption argument

Comments on Preemption of State Warning Requirements Proposal

1. The document makes frequent reference to the term "rational prescribing". This is not a term that I am familiar with in the regulatory context and I don't know if it exists somewhere in our statute or our regulations that I am overlooking. I believe FDA's goal for labeling is to provide the physician (and in some cases the patient) with the available information for the drug product that is needed to inform safe and effective use of the drug for the approved indications. The use of the term "rational prescribing" concerns me since it implies that the FDA approved label provides the ONLY information that is needed to inform "rational prescribing". That obviously is not true; the most obvious example is off-label use(s) of the drug that may be appropriate medical care, but for which FDA has not received an efficacy supplement from the sponsor. It would be mistaken to say that prescribing the drug for such an off-label use is not "rational prescribing". Granted, the FDA approved labeling would provide information that would be useful to help direct such off-label prescribing (e.g., common adverse events), but it cannot provide all the information to help inform such use.

2. The premise of the basis for much of the argument for why we are proposing to invoke preemption seems to be based on a false assumption that the FDA approved labeling is fully accurate and up-to-date in a real time basis. We know that such an assumption is false. Even if the sponsor exercises due diligence to identify new risks after approval of a drug and submits requested changes in risk information to FDA in a timely manner, there will always be a delay before such information appears in the package insert, even in the case of a CBE supplement. So, it is unwise to suggest that FDA approved labeling is always up-to-date and always contains a full and complete listing of all pertinent risk information. Even in the best case scenario of a diligent sponsor and a CBE supplement, the new risk information will not be available in the bottle or in printed material like the PDR for some

period of time.

3. In the background section of the document we argue "Manufacturer have product liability-related incentives to include exaggerated statements of risk information in labeling." I think this is a gross overstatement of the reality of what we see in working with sponsors regarding adding risk information to labeling. In my experience, the opposite is often the case; i.e., we more often find that sponsors disagree with our recommendations for how prominent warnings and precautions should be and suggest alternative language that lessens the impact of the warning. This is true in many cases where FDA recommends a boxed warning for example. It is not unusual for sponsors to argue strongly that a boxed warning is not needed and that the risk information can be appropriately displayed as simply a warning or a precaution. In some cases we agree with the sponsor's argument, but it has been very rare in my experience (I cannot actually recall a case) where a sponsor has requested the addition of a boxed warning that we did not think was warranted. The proposal may be making reference to requests to add specific adverse events to the adverse events section of labeling to address concerns about liability and failure to warn. I have seen cases where sponsors have specifically asked to include a "laundry list" of adverse events to the labeling and in some cases they have insisted that such a list is needed for liability protection. On the other hand, I have also worked with many sponsors who have readily accepted FDA's preferred approach to limiting the inclusion of adverse events in the labeling to those that occur at a reasonable frequency and appear to be plausibly related to the drug. In some cases I believe that a motivating factor for sponsors who wish to include the "laundry list" is based on a desire to lessen their adverse event reporting burden (i.e., if the adverse event is "labeled" the reporting requirements to FDA are different) as much or more so than to limit liability concerns. The entire argument put forward that sponsors are insisting on exaggerated statements of risk information is naive to what actually occurs in practice. While I do not believe that most sponsors deliberately attempt to obscure risk information about their products in the product labeling, I also believe it is true that sponsors attempt to present the information in a way that does not put their product at a competitive disadvantage to other products. I certainly have not seen cases where sponsor have deliberately exaggerated risk information in boxed warnings, warnings, precautions, contraindications, etc. due to liability concerns.

4. On page 5, there is a statement that "...the approved labeling, which reflects thorough review of the scientific evidence and communicates to health professionals the agency's formal, authoritative conclusions regarding the conditions in which the product can be used safely and effectively." This is an overstatement since we only review those proposed uses that are submitted by the sponsor. In many cases drugs can be and are used to safely and effectively treat conditions other than those in the approved labeling.

5. On page 6, there is a statement that "It does not properly include statements of theoretical hazards." While this is true in theory, many approved labels include warnings or contraindications based on theoretical hazards. The most common is a contraindication in patients who are hypersensitive to the product in the absence of any evidence that hypersensitivity occurs. We also frequently include risks associated with similar drugs that have not been reported for the particular drug.

6. Also on page 6 is a footnote about intended purpose. I am concerned that sponsors could use preemption as a way to "hide behind" a label that is limited to a narrow indication that may involve less risk than the wider indication for which the drug will be used. While sponsors already sometimes target the "easy" indication for approval first (e.g., most bisphosphanates are approved first for Paget's disease and later for osteoporosis) they still have a strong incentive to seek

the further indication. If they know that they have liability protection for the approved indication it may alter the dynamic somewhat of the incentive for getting new indications approved. They could rely on off-label prescribing and feel protected because they are not promoting the drug for such use.

7. The discussion of CBE supplements for new safety information is not accurate. On page 8 it says that "If a manufacturer adds or strengthens a statement of risk information without at least consulting with FDA in advance, it risks that they agency will disagree that the statement is appropriate. If FDA does disagree, the agency could initiate enforcement action on the ground that the labeling is false or misleading or fails to provide adequate directions for use. In practice, therefore, manufacturers do not exercise their entitlement to add risk information to labeling pending FDA's evaluation of the change." Each statement is misleading or incorrect. Sponsors sometimes discuss a CBE with us in advance, but that is far from the norm. We often review CBE supplements and decide that we think changes are warranted; rarely that the added statement is not appropriate. I don't know of any example where we have taken enforcement action. Rather, we send the sponsor a letter either approving or not approving the change. In most cases we negotiate new wording that is then incorporated into the labeling. To say that sponsors don't send in CBE labeling supplements is not correct based on the data. Per COMIS, we receive a large number of CBE labeling supplements each year. While not all of these are safety related (CBE supplements can also include minor editorial changes) it is pretty clear that the last statement cited above is not correct (the %CBE category is calculated based only on those where the CBE/PA field in COMIS was completed by the division and given the large number of NotDesignated SLRs is not reliable).

FY	# SLRs	CBE	PA	NotDesginated	% CBE
2001	701	289	81	331	78%
2002	655	267	96	292	74%
2003	439	186	92	161	67%

I know of no evidence to support a conclusion that sponsors do not submit CBE labeling supplements for safety issues.

8. On page 9 it says "FDA regulation of the dissemination of risk information in prescription drug and biological product labeling thus effectively operates as both a "floor" and a "ceiling." I do not agree since sponsors can and do add new safety information without FDA prior approval.

9. Much of the data in the liability section seems to be very old, anecdotal, or conveniently missing but still used to support the argument. The use of such old data begs the question of why now? If this has been such a big problem for so long, why is FDA only now taking up this issue?

10. On page 13 it states "…First, they warn against all conceivable risks associated with a product, whether or not such risks have been scientifically substantiated by data from clinical trials or postmarketing experience." This is simply wrong and the only "data" given to support the statement is some citation to an article in some law journal. Even sponsors who insist on the "laundry list" of adverse events do not include all "conceivable risks" and certainly they don't insist that we include a boxed warning on their product. On this page,

the document also suggests that the primary reason for sponsors not developing products for small populations is liability concerns, but it completely ignores the fact that such products also will have small SALES! I also find the arguments that the price of the drug is determined by the liability risk to be very dubious and the comparison of the price in Canada to the price in the US and the conclusion that the liability concern is the primary cause of the differential is laughable.

11. On page 17 there is a suggestion that doctors don't prescribe drugs that are the only available drug in a class because they have been warned away by the risk information. This is laughable. One of the examples given is XIGRIS. I know of no data (and none is provided) to support a conclusion that doctors are not prescribing this because of the "exaggerated" warnings of risk information. Rather, I think the low prescribing rate is more likely a reflection of the limited efficacy seen in clinical trials and the cost of the drug.

12. I'm not sure what criteria were used to conclude that the labeling statements in the table on page 18 are "incomplete, obsolete, or exaggerated." I think we are all aware of issues related to how to label drugs for use in pregnancy, but many of the issues are scientific and data-limited, not simply liability issues.

Morton, Patreese E (CDER)

From: Jenkins, John K
Sent: Wednesday, June 18, 2003 9:55 AM
To: Axelrad, Jane A; Woodcock, Janet; Galson, Steven
Cc: Temple, Robert; Behrman, Rachel E; Jenkins, John K
Subject: RE: Consolidated comments on product liability draft

Jane

I'm in general agreement with the edits that you, Bob, and Rachel have made to this document (I say general because it is hard to keep track of the document and all the changes from various editors without reading it on the screen, and that makes it tough to follow). I would offer some general comments for future versions:

1. I agree with the idea that we should preempt state requirements for labeling of drugs. It makes no sense for us not to have a federal system for labeling approved drugs that is based on a careful scientific review of the available data and a consistent application of labeling policies across products. I see this as a legitimate FDA area of involvement given our statutory authority over the drug approval process.

2. I am not so comfortable with the whole argument in the document about preempting state liability cases against a manufacturer for "failure to warn" cases. I'm not sure why this falls within FDA's purview (are there any other examples of where FDA has promulgated regulations based primarily on a desire to protect sponsors from liability?) and I think the whole argument that liability concerns drive inaccurate labeling is false and misleading (we control the text of labeling, even in the case of CBE supplements we have final authority) and the whole argument that liability concerns lead to decreased product innovation or product withdrawals is not supported by adequate data. It seems that if we are going to preempt individual patient's ability to hold a sponsor liable, we should have pretty strong data to support the fact that our action is in the interest of public health. We are proposing to take away rights of an individual, presumably for the greater public good, and I think the standard of evidence for such an action should be high (isn't that what Constitutional purists think?). Such a high bar is not met by the arguments in this document. I recognize the conundrum of trying to reconcile my support for #1 and my lack of support for #2; i.e., if labeling is the primary way of communicating information about safe and effective use and the labeling is controlled by FDA how can the sponsor be held liable for failure to warn. I guess I feel much more comfortable with such a defense if FDA has specifically reviewed data and determined that its addition to the labeling is not warranted (I think that was the California Paxil case). Of course, this pathway could lead us to being swamped with data to support warning statements so the sponsor could document a denial by FDA or could lead us to being dragged into every court case to render a judgment on the data. This is clearly an area the requires some sort of compromise, but so far the proposed document is tilted totally in favor of the sponsor over the individual patient.

3. I continue to be concerned that compliance with FDA reporting requirements is not enough to make the preemption pathway a viable option (if it indeed goes forward). If we are going to be held up as the final arbiter of labeling information, we need more power to dictate labeling language than we have today. Otherwise, sponsors can be in full compliance with reporting and simply stonewall us on any needed labeling changes that they do not like. As an example, we have been negotiating with [redacted] for several months on what labeling text to include for [redacted] and [redacted] as a result of the [redacted] study that showed a safety signal for serious and life-threatening adverse events. This had made it all the way to Janet, who supported our position, but we still have little power to force [redacted] to make these changes. Under preemption they would be protected since it is not in the FDA approved labeling. So, if we are going to go this route to protect sponsors, the appropriate balance in the favor of public healthy may be to give FDA more authority over labeling.

John

-----Original Message-----
From: Axelrad, Jane A
Sent: Sunday, June 15, 2003 12:17 PM
To: Woodcock, Janet; Galson, Steven; Jenkins, John K
Cc: Temple, Robert; Behrman, Rachel E
Subject: Consolidated comments on product liability draft

Attached is a set of consolidated comments: mine, Bob's, and Rachel's. I went over the comments and rejected a few (some were comments on comments) and left in the ones I agreed with (most). I have several conflicting comments from Bob and Rachel that we need to discuss.

Do you all want to convey anything else to Dan? I thought it would be good to send one set of comments from CDER

Monday, if possible. Thanks.

On my screen: I'm green, Bob's pink, Rachel's red. I still have to add some comments to the legal section. I have to do that, pun intended, judiciously!

Jane

<< File: reopenerred.doc >>

Axelrad, Jane A

To: Daniel Troy (E-mail); Klasmeier, Coleen
Cc: Woodcock, Janet; Shuren, Jeff; Lorraine, Catherine C; maloney, diane
Subject: CLOSE HOLD: PRODUCT LIABILITY

Dan and Coleen:

As we discussed with Dan today, here are CDER's consolidated comments on the preemption document. I tried to incorporate in some places the arguments Dr. Woodcock was making about our standards and the application of the evidence to the standards but more needs to be done in this regard. I hope that we will be able to sit down and look at the big picture theories behind this (how we are casting the document in terms of requesting comments and how we are describing and justifying preemption in terms of FDA's full occupation of the field) so that we can be sure the document reflects a consistent message and a cohesive theory on preemption. As Jeff said, this draft of the document was much better than the previous draft and I'm sure the next version will be even better. Please call if you have questions or need additional information.

Jane

cderreopener.doc

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DRAFT – June 6, 2003

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 00N-1269]

RIN 0910-AA94

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Reopening of the Comment Period

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; reopening of the comment period.

SUMMARY: The Food and Drug Administration (FDA) is reopening to [*insert 60 days from date of publication in Federal Register*] the comment period for a proposed rule published in the **Federal Register** of December 22, 2000 (65 FR ~~81082).~~81082) . In that document, FDA proposed to amend its human prescription drug and biological product labeling regulations to: (1) require that the labeling of new and recently approved products include sections containing highlights of and an index to prescribing information; (2) reorder and make minor changes to the content of currently required information; and (3) establish minimum graphical requirements for labeling.~~The purpose of the proposed rule is to make it easier for health care practitioners to access, read, and use information in prescription drug labeling and enhance the safe and effective use of prescription drug products. For indications for which the sponsor has elected to submit safety and effectiveness data, and to the extent that the sponsor has complied with the act's requirements for the submission of pre- and post-marketing safety data and Phase IV data to FDA, labeling provides authoritative information on the circumstances in which an approved~~

Although these regulations (21 CFR 201.57-.58) have remained largely unchanged since their promulgation in 1979, our application of them in practice has evolved. Through the issuance of numerous detailed interpretive guidelines [through notice and comment rulemaking??] and our role as the approver of both the initial drug labeling as part of an NDA or BLA and any post-marketing changes to the labeling, we have asserted more and more control over labeling. As discussed in Part I of this document, we carefully control every statement in the package insert through the approval process. We also monitor clinical experience following marketing and require manufacturers to amend risk and other information in labeling as necessary. This next sentence switches back to legal argument and doesn't work here. Our prescription drug and biological product labeling requirements are as comprehensive, at least, as our regulations governing the content and format of labeling for medical devices, which four Members of the Supreme Court have found preempt state failure-to-warn claims. [But this was based on a specific Federal statute preempting!!] (*Medtronic*, 518 U.S. at 514 (O'Connor, J., joined by Rehnquist, C.J., Scalia, J., and Thomas, J., concurring in part and dissenting in part).)

Within the past several years, we have become concerned that state product liability lawsuits could require manufacturers to include in labeling risk information not supported by data that hayes not been scientifically substantiated and is not part of a summary of the essential scientific information needed for the safe and effective use of the drug. [Our experience hasn't shown this. Companies rarely press for meaningful risk information or additional warnings. And they always oppose black box warnings. Much of the discussion of what goes in the label centers around the sponsors wish to promote the drug fully and to not be handicapped by ~~substantiated.~~risk information that would have to be conveyed in ads. Sponsors do seek to

increase the reactions in the Adverse Reactions section because this influences their reporting requirements (if it's in the label, it is an expected event and reporting requirements are less).]

Under our 1979 prescription drug labeling regulations, a manufacturer must include in labeling "the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable." (21 CFR 201.57(g)(1).) The regulation defines "adverse reaction" as "an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." (21 CFR 201.57(g).) FDA has determined that the "reasonably associated" language "can be and in many cases has been interpreted as meaning that a reaction should be included merely if there is a temporal association, rather than a reasonable causal association, between a response and a drug. As noted above, manufacturers have increasingly been seeking to list more events in the 'Adverse Reactions' section of ~~labeling that is~~labeling. These listings of adverse events are not meaningful to prescribers and ~~which dilutes~~dilute the usefulness of the clinically meaningful information." (65 FR at 81094.)

FDA has determined that the standard for disclosing risk information in labeling should be changed. In June 2000, we issued a draft guidance document (65 FR 38563; June 21, 2000) discouraging sponsors from including every conceivable adverse event about a drug in product labeling:

> In general, the ADVERSE REACTIONS section should include only information that would be useful to clinicians when making treatment decisions and in monitoring and advising patients. Long and exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy, or not plausibly related to drug therapy, should be avoided.

Morton, Patreese E (CDER)

From: Jenkins, John K
Sent: Wednesday, August 06, 2003 8:22 AM
To: Axelrad, Jane A; Temple, Robert; Behrman, Rachel E
Cc: Jenkins, John K
Subject: RE: proposed reopener of the physician labeling rule

Jane

Here are my comments on the new draft. As we discussed yesterday, I am providing general comments rather than line-by-line edits:

1. The draft is written from a very pejorative tone and does not present a fair and balanced assessment of the issues related to preemption. In many places the draft makes reference to the "increasingly comprehensive federal regulation of drugs" and in the summary states that the proposed PLR "will make the already broad and high prescriptive drug regulatory scheme under the Federal Food, Drug, and Cosmetic Act even more detailed and comprehensive. I see very little evidence presented in the document to support our "increasing comprehensive regulation of labeling". The document tone suggests that the proposed PLR has already been finalized as evidence to support this claim. Other than the proposed PLR, they provide very little evidence that we have changed our regulation of drug labeling since 1979. The only evidence that I can find other than the proposed PLR are references to draft guidances on the content of various sections of the physician labeling. Given the clear disclaimers in guidances about their non-binding nature I don't understand how they can be held up as examples of our "increasing...regulatory oversight of prescription drug labeling" (see page 4). Furthermore, the entire argument about the effects of the proposed PLR seem to be overstated not only considering the actual effect of the rule, which in many ways represents a reordering of sections plus the addition of a highlights section, along with the fact that the new rule will NOT impact on the vast majority of drug labels (at least not initially) given its narrow application to new and recently approved labels.

2. I see little if any relationship between the proposal for the Agency to state its views on preemption and the proposed PLR and therefore see little reason why this new initiative should be linked to the proposed rule. In my mind they should be severed since it is clear that the proposal on preemption would exist even in the absence of the proposed PLR.

3. The draft makes reference to our "virtually plenary authority over drug labeling" and states that we "precisely control" the content and format of package inserts (see page 3). This seems to be a major overstatement of the facts and actual situation. While at a high level such statements may be true, we know that many current approved drug labels are out of date and in many cases contain incorrect information (e.g., the overdose section). Also, if we have so precisely controlled the content and formal of drug labeling you have to wonder how we managed to develop a backlog of over 1000 labeling supplements during the same time that we were very focused on implementing the PDUFA goals. While we have eliminated that backlog, its mere existence for many years and the fact that we continue to go "overdue" on labeling supplements and to take up to 6 months to review even minor changes questions how "precisely" we perform this function.

4. At the top of page 4 there is a statement that "Consequently, drugs are currently subject to legal liability for violation of both state and federal law." I think they mean that sponsors or manufacturers are subject to legal liability.

5. On page 4 and in other places there are continued references to sponsors "disclosing too much" risk information and its adverse impact on rationale pharmacotherapy. I think our concern is more that the risk information be accurate and balanced and we rarely find ourselves in situations where sponsors want to disclose more risk information than we think is necessary. To the contrary, we usually find ourselves dealing with situations where sponsors wan to minimize the risk information (e.g., the recent debate with [redacted] about the boxed warning for [redacted] and [redacted], which required Janet's intervention).

6. On page 5 and in other places in the document there are references to uses of a drug

in individual patients "that FDA has determined would be safe and effective." Our evaluation of drugs is based on data from clinical trials and our labeling is derived from those data. The labeling is intended to provide doctors with the information needed to safely and effectively use drugs to treat patients, but the labeling is not intended to define safe and effective use in individual patients. That falls to the practice of medicine.

7. On page 6 it says that the need for "FDA involvement in these cases is increasing." I see no data to support this statement.

8. The discussion of the possibility of linking the preemption to compliance on page 7 and in other places is not presented in a fair and balanced way. For example, we open the discussion of this issue on page 7 with the statement "FDA also seeks comment on whether there are any impediments to stating that ....." This presents the possibility of a compliance link in a negative way and I can see very little in the document where they ever show the positives of such a link. Also, they seem to suggest that the preemption should apply to off label uses unless the sponsor has "improperly promoted the particular approved drug at issue for an off-label indication." Its not clear to me how FDA can be responsible for assuring that all relevant risk information for off-label uses is in the labeling if the indication has not been proposed to us and it is also not clear how we would enforce the "improperly promoted" clause. We know that companies do off label promotion all the time. It would seem more reasonable to link preemption to labeled uses only and this would serve as an incentive for sponsors to get new labeled indications. Also, the Phase 4 commitment issue is much more complex than the simple way it is stated in the draft. There is no discussion of how we would make determinations about whether sponsors have "made a substantial good faith effort" to meet their commitments.

9. On page 11 there are data related to safety drug withdrawals. The implication is that FDA withdrew these approvals, the reality is that all were voluntary suspension of marketing by the sponsor.

10. On page 12 there is a statement that "Manufacturers generally consult FDA before adding risk information to labeling.." I don't know what this statement is based on and it is not in agreement with the large number of CBE labeling supplements to add risk information that we receive each year.

11. The draft contains discussion on page 15 of the definition of adverse events for labeling. Doesn't the new draft final rule go back to the old definition?

12. On page 21 there is discussion of the Cardura case and the implication is that FDA is constantly monitoring the literature and that we force sponsors to add new risk information whenever we see a study that suggests one drug may be better than another. Nothing could be further from the truth. We would take such action only in extraordinary cases and we generally have a very high standard for adding comparative claims to the labeling. In the same paragraph there is reference to FDA requiring a sponsor to issue a DHCPL. Our regulations give us the authority to ask a sponsor to send such letters and state how such letters should be sent (e.g., envelope titles), however, the regs do not give us the authority to require such communication.

13. On page 23 there is the statement that "FDA believes manufacturers should add risk information to labeling only after consulting with the agency...." This is not true and is not consistent with our CBE regulations. Granted we review CBE supplements, but we do not discourage sponsors from adding new risk information via this route. In fact, the regs encourage use of this route as it allows the label to be updated in the most timely manner.

14. On page 25 there is discussion about "defensive labeling". As noted earlier this is not the scenario we usually encounter unless they mean cases where sponsors try to "defend" their product by minimizing important risk information.

15. On page 26 there is a statement that "labeling that contains multiple statements of information to satisfy state authorities will be unusable by health professionals." I see no data to support this overly broad statement. Such labeling may be confusing, but I think it is wrong to say it will be unusable.

16. The whole section #2 starting on page 26 is very confusing and I found it hard to read and follow. Maybe you need to a lawyer and an economist to understand this section, but I

could not.

17. The statement on page 30 about the availability of drugs for nausea is misleading, what they mean is that we don't have drugs specifically indicated for nausea in pregnant women. Women do have access to these drugs for off label use.

18. On page 18 there is reference to "baseless" product liability suits. I don't see data to support use of such a strong pejorative term.

19. I don't understand the logic of the statement on page 45 that preemption will give sponsors the incentive to conform their labeling to FDA regulations. First, the entire document has suggested that we regulate labeling with zealous fervor so it is hard to understand why preemption would be needed to ensure compliance with the proposed PLR. It also goes against the oft stated argument that sponsors are already over warning.

20. On page 47 there is a suggestion that post marketing safety reporting is already poor by many sponsors. If this is true, it is not clear to me how preemption will make this better. The paragraph starting at the bottom of page 47 and extending to page 48 makes no sense to me at all. I don't understand how all these concepts link to preemption, particularly the one about improving our first cycle review performance.

21. The section on the preemptive effect of FDA regulation of drugs under the act that starts on page 52 seems to suggest that we have already decided the issue of preemption and begs the question of why we are asking for comment on the proposal. A more fair and balanced assessment of preemption would be more appropriate unless we have already made up our mind and are simply supporting our case.

Overall, while they have made many of the changes we suggested, I still find the arguments in support of preemption weak and I do not see enough discussion of the pros and cons of linking this to preemption. It also strikes me how "elastic and plastic" our arguments have been over the various drafts despite the fact that they always get us to the same, apparently foregone conclusion.

John

-----Original Message-----
From: Axelrad, Jane A
Sent: Wednesday, July 30, 2003 5:30 PM
To: Jenkins, John K; Temple, Robert; Behrman, Rachel E
Subject: FW: proposed reopener of the physician labeling rule

The latest greatest. Close hold, as before. Janet and I are the only other CDER folks that have it.

-----Original Message-----
From: Troy, Daniel
Sent: Wednesday, July 30, 2003 4:53 PM
Subject: proposed reopener of the physician labeling rule

Attached please find a revised draft of the liability paper. I apologize for the delay in sending it around. We have tried to accomodate as many comments as possible. We think this is the most sustainable position while still accomplishing the policy goals we all share. This document is nearing its final form, but we still seek your views, and no final decisions have been made about it. (Consider this the penultimate draft.) Please direct your comments to me and to Coleen Klasmeier by August 6. Thanks so very much in advance.

Morton, Patreese E (CDER)

From: Axelrad, Jane A
Sent: Thursday, August 07, 2003 3:54 PM
To: Troy, Daniel; Klasmeier, Coleen
Cc: McClellan, Mark, M.D.; Woodcock, Janet; Galson, Steven
Subject: Reopener

Dan and Coleen:

CDER appreciates the opportunity to comment again on the "reopener" document. Although you have made many of the changes we suggested, the document still needs work. Last time we commented, we did line edits of the document. This time, we are providing big picture comments and may send additional line edits but would prefer to work with you on line edits after the larger necessary revisions are made.

1. The "reopener" document, as it is now drafted, has no real connection with the physician labeling rule and should be issued as a stand alone request for comments or advance notice of proposed rulemaking. This draft says, "we are considering whether to publish in the Federal Register a single, comprehensive document setting forth FDA's policy that federal law relating to the safety, effectiveness, and labeling of drugs is the exclusive source of regulation in this area and that different or additional state requirements threaten the agency's ability to carry out our statutory mandate and harm the public health." (p.6). It doesn't say we are thinking of amending the physician labeling rule, it doesn't contain any codified language, and it isn't connected in any way to any comments on the rule. Since it has no connection with the rulemaking, it should be separated from it and travel on its own. There is no reason to believe the document will move more quickly connected to the physician labeling rule (which still has to go through Agency, Department, and OMB clearance), particularly since the plan is to issue the reopener immediately while the rule travels through clearance. Moreover, the "reopener" has the potential to bog down the final rule if we get a lot of adverse comments on the preemption policy.

2. The document needs to be revised to state clearly what we are proposing to do and what we are seeking comment on. Below I've attached the language taken from the document that reflects the variety of different ways we've stated what we are proposing to do and what we are asking for comment on. These are so varied, it is hard to fathom how someone seeking to comment on the document will figure out what we are proposing to do.

3. Although styled as a request for comment, the document is really an advocacy piece for preemption. If that is what it is, it should be revised and issued as a statement of policy on which we are soliciting comments. This comes through particularly clearly in section III, Solicitation of Comments, (pp. 39-49) where it asks for comment on the first page, proposes a statement of policy on the next, and then goes on for over 8 pages advocating federal preemption. If the document isn't really an advocacy piece, then it should be more neutral in its presentation of the arguments for and against preemption. And if it is, it should say so and ask for comments on the position.

4. The discussion of the possibility of linking the preemption to compliance on page 7 and in other places is not presented in a fair and balanced way. For example, you open the discussion of this issue on page 7 with the statement "FDA also seeks comment on whether there are any impediments to stating that ....." This presents the possibility of a compliance link in a negative way and there is very little in the document that shows the positives of such a link. The document also seems to
suggest that the preemption should apply even to off label uses unless the sponsor has "improperly promoted the particular approved drug at issue for an off-label indication." Preemption should not apply to off-label uses since the premise that we have carefully reviewed all the data and made sure the label reflects all of the

information necessary for the safe use of the drug does not apply to off-label uses. Furthermore, by allowing preemption even for off-label uses, the document undermines the incentives to get information into the approved labeling that would otherwise exist were preemption limited to uses in the approved labeling.

5. The section on pages 26-39 is very hard to read and follow. It is full of pejorative references to FDA (e.g., the FDA drug approval is so stringent that there is "excess investment in the avoidance of adverse drug events," "the FDCA, as administered by FDA, induces excessive product safety,") and uses terminology that is out of place in an FDA document (e.g., "inefficient injuries"). The document argues that FDA regulation is overly burdensome at the same time it relies on the comprehensive nature of FDA's regulation to support the preemption argument. We have repeatedly said that cost of loss of Bendectin is greatly overstated, and this example is very weak.

6. The draft makes reference to the "increasingly comprehensive federal regulation of drugs" and in the summary states that the proposed physician labeling rule "will make the already broad and high prescriptive drug regulatory scheme under
the Federal Food, Drug, and Cosmetic Act even more detailed and comprehensive." But the document contains little evidence to support our "increasingly comprehensive regulation of labeling." Other than the proposed physician labeling rule (PLR), the document cites little evidence that we have changed our regulation of drug labeling since 1979. The only evidence cited in the document other than the proposed rule are references to draft guidances on the content of various sections of the physician labeling. Given the fact that guidances are non-binding (as we are frequently reminded), they shouldn't be held up as examples of our "increasing...regulatory oversight of prescription drug labeling" (see page 4). Furthermore, the entire argument about the effects of the proposed PLR seem to be overstated considering the actual effect of the rule, which in many ways represents a reordering of sections plus the addition of a highlights section. In addition, the new rule will NOT affect the vast majority of drug labels (at least not initially) given its narrow application to new and recently approved labels.

7. On page 4 and in other places there are continued references to sponsors "disclosing too much" risk information and its adverse impact on rational pharmacotherapy. Our concern is more that the risk information must be accurate and balanced. We rarely find ourselves in situations where sponsors want to disclose more risk information than we think is necessary. To the contrary, we usually find ourselves dealing with situations where sponsors want to minimize the risk information (e.g., the recent debate with [redacted] about the boxed warning for [redacted] and [redacted], which required Janet's
intervention).

8. On page 5 and in other places in the document there are references to uses of a drug in individual patients "that FDA has determined would be safe and effective." Our evaluation of drugs is based on data from clinical trials and our labeling is derived from those data. The labeling is intended to provide doctors with the information needed to safely and effectively use drugs to treat patients, but the labeling is not intended to define safe and effective use in individual patients. That falls to the practice of medicine.

9. The draft contains discussion on page 15 of the definition of adverse events for labeling. But as we indicated in our last set of comments, the new draft final rule goes back to the old definition. This MUST be changed.

10. On page 21 there is discussion of the Cardura case and the implication is that FDA is constantly monitoring the literature and that we force sponsors to add new risk information whenever we see a study that suggests one drug may be better than another. Nothing could be further from the truth. We would take such action only in extraordinary cases and we generally have a very high standard for adding comparative claims to the labeling. In the same paragraph there is reference to FDA requiring a sponsor to issue a Dear Health Care Professional Letter. Our regulations give us the authority to ask a sponsor to send such letters and state how

such letters should be sent (e.g., envelope titles). However, the regs do not give us the authority to require such communication.

11. On page 23 there is the statement that "FDA believes manufacturers should add risk information to labeling only after consulting with the agency...." This is not true and is not consistent with our CBE regulations. Granted we review CBE supplements, but we do not discourage sponsors from adding new risk information via this route. In fact, the regs
encourage use of this route as it allows the label to be updated in the most timely manner.

Various Requests for Comment In the Document

Page 1:

"FDA is reopening the comment period to invite public comment on the effect of increasingly comprehensive federal regulation of drugs on certain requirements under state law. Specifically, FDA is soliciting comment on what actions, if any, the agency should take to clarify its views with respect to preemption of state common law and legislative requirements by federal law, to obviate the need for the agency to safeguard its role as the sole regulatory agency responsible for evaluating the safety, effectiveness, and labeling of prescription drugs through resource intensive case-by-case participation in judicial proceedings. FDA seeks comment on whether any policy established in this area can and should make clear that the exclusivity of federal law in the drug area rests upon the agency's receipt of sufficient information regarding the safety and effectiveness of products to reach proper regulatory decisions (i.e., where manufacturers have submitted substantial evidence of safety and effectiveness for the intended use at issue, have substantially complied with pre- and post-marketing requirements, and have met Phase IV study commitments)."

Page 6:

"We are considering whether to publish in the Federal Register a single, comprehensive document setting forth FDA's policy that federal law relating to the safety, effectiveness, and labeling of drugs is the exclusive source of regulation in this area and that different or additional state requirements threaten the agency's ability to carry out our statutory mandate and harm the public health."

Page 7:

"Accordingly, FDA also seeks comment on whether there are any impediments to stating that preemption should not be available to persons and entities that have improperly promoted the particular approved drug at issue for an off-label indication, provided material false information, failed to include material safety and effectiveness data in an NDA or BLA, failed to provide required post-marketing information material to the safe use of the product, or have not made a substantial good faith effort to conduct Phase IV studies to which the applicant submitted (i.e., studies for which the status is delayed under 21 CFR 314.81(b)(8) or 601.70(b)(8) (see 65 FR 64617 and 64618; October 30, 2000))."

Page 8:

"the agency is now considering issuing a statement of policy addressing the relationship between federal and state law. This would enable FDA to increase reliance on private litigants to bring the agency's preemption policy to the attention of state courts and other appropriate authorities, reducing the need for resource-intensive case-by-case participation."

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 7, 2004

FROM: Steven Galson, M.D., MPH
Acting Director, Center for Drug Evaluation and Research, HFD-001

SUBJECT: Physician Labeling Rule

TO: Dan Troy, Esq.
Chief Counsel, GCF-1

We have completed our revision of the physician labeling final rule and accompanying preamble based on your comments. We have made a concerted effort to accept your suggested changes, not only those focused on legal sustainability, logical coherence and clarity, but also those that we believe reflect editorial preference. In addition, we have incorporated substantial revisions according to the over-arching principles apparent from your comments and edits (e.g., avoiding explicit reference to flexibility, emphasizing that labeling must contain the information necessary for safe and effective use). We were not able, however, to accept all suggestions, in particular if the intended meaning appeared to be unintentionally changed.

For ease of reference, we are providing:

- A "clean copy" of the draft final rule and preamble
- A version comparing the draft final rule and preamble to the version you provided to us on 4/19/04
- Table 1, from your memorandum dated 3/30/04, annotated with our response to each comment

In response to the issues outlined in your memorandum dated March 30, 2004, I offer the following comments:

I. Necessary for Safe and Effective Use

The draft has been substantially revised to emphasize that the information required to be included in labeling is necessary for safe and effective use.

II. Optional and Recommended Disclosures

In accordance with agreements reached at the 5/17/04 meeting between yourself and members of my staff (Rachel Behrman and Janet Norden), in most cases it has been possible to revise the draft codified in such a way that requirements are stated as absolutes ("musts"). These are, in some instances, followed by a list or description of exceptions. In a few cases, the flexibility necessary for the Centers to develop logical and useful labeling cannot be achieved without the use of discretionary language ("mays").

III. Technical Issues

- The National Drug Code number is not required in 201.57(c)(17) "How Supplied/Storage and Handling," but is listed as an example of appropriate information to facilitate identification of the dosage forms. We do not believe that your revision of the draft codified alters this. However, to minimize confusion, we have deleted the reference to 201.57(c)(17) from 201.57(c)(4) "Dosage Forms and Strengths."

- We agree with your approach to consolidating references to patient information under a single term and have amended the draft final rule accordingly.

- We acknowledge your concern that the requirements for one section should not be restated in another section and have achieved our intended goal (to distinguish between sections where more or less detail is required) through changes in wording.

- As agreed at the 5/17/04 meeting, the draft has been revised to specifically state in any applicable sections where an explicit mention of "lack of information" is needed because the absence of such data are important for the safe and effective use of the drug.

- We have retained language reiterating statutory or regulatory obligations only in those places where we believe it is critical for emphasis and clarity.

In addition, I should note that there were two issues with which we are unable to concur, for the reasons discussed below.

- Preemption
  We have declined to include the section on preemption. We had agreed that would be handled separately from this rule, and we worked with you on a separate guidance. As including such a section at this point in this rulemaking is likely to be quite controversial, and may make the rule vulnerable to legal challenge, we do not want to include it. We address the product liability concerns expressed in the comments by stating that we believe that inclusion of Highlights will be a more effective format for warning practitioners about a product's safety profile, and we have added statements to emphasize that the Highlights do not contain all the information necessary to safely prescribe the drug.

- Intended Use
  We have not made the changes you suggest regarding intended use. Adding language to clarify that drug labeling contains information only pertaining to the drug's "intended use" could be read to unnecessarily restrict FDA's authority to address safety and efficacy concerns that might arise through conditions of use that are customary and usual, but not under the approved indication. The current language has been on the books since 1979, mirrors the statutory authority for labeling, and, to our knowledge, has not been seriously challenged.

We would be happy to discuss.

Attachments:
(1) Clean copy of the draft final rule
(2) Compare version of the draft final rule
(3) Clean copy of preamble
(4) Compare version of preamble
(5) Table 1

cc: Janet Woodcock, M.D.

CDER Office of Regulatory Policy (HFD-7) Routing Slip	Date August 6, 2004		
1. Concurrent: S. Galson (HFD-1)			8.6.04 (w/ exceptions)
J. Goodman (HFM-1)			
2. A. Wion (GCF-1)			
REVIEW DRAFT	X	FINAL CLEARANCE	

REMARKS

REVIEW OF REVISIONS BASED ON OCC COMMENTS

Federal Register- Final Rule

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products

Also attached:
- Copies of Center clearances from 8/03 and 9/03
- Federal Register Document Final Clearance Record

Exceptions:
CDER remains concerned about the scope of the pre-emption comments (#12 and 13) and questions their inclusion in this rulemaking.

COMIS #: 4264 FRDTS #: CDER012

FROM: (Name, office symbol)	Room No. – Bldg. 1101 – RKW 2
Liz Sadove (HFD-7)	Phone No. 301-443-5540

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CDER Office of Regulatory Policy (HFD-7) Routing Slip	Date August 6, 2004
1. Concurrent: S. Galson (HFD-1)	
J. Goodman (HFM-1)	Per Goodman 8/6/04 see comment
2. A. Wion (GCF-1)	

	REVIEW DRAFT	X	FINAL CLEARANCE		

REMARKS: CBER concurs with this version of the labeling rule with the exception that we believe that the preemption policy statements (e.g. Comment 13), while addressing very significant public policy and regulatory issues and having a number of merits, should be moved forward for consideration as a separate document and not included within the labeling rule which has a distinct medical/scientific informational focus and history.

REVIEW OF REVISIONS BASED ON OCC COMMENTS

Federal Register- Final Rule

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products

Also attached:
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COMIS #: 4264 FRDTS #: CDER012

FROM: (Name, office symbol) Room No. - Bldg. 1101 - RKW 2

Liz Sadove (HFD-7) Phone No. 301-443-5540

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Preemption Section-
PLR comments

Axelrad, Jane A

From: Behrman, Rachel E

Sent: Wednesday, August 10, 2005 2:34 PM

To: Woodcock, Janet; Shuren, Jeff

Cc: Galson, Steven; Goodman, Jesse; Axelrad, Jane A; Maloney, Diane; Throckmorton, Douglas C; Sadove, Elizabeth; Norden, Janet M; Beakes-Read, Virginia G

Subject: Comments by the PLR working group on the revisions to the preemption section from OCC

General Comments

As noted by Drs. Goodman and Throckmorton on the original transmittal sheets, the centers believe that an extensive discussion of preemption should not be included in this rule. The question of preemption is tangential to the purpose of this rule and any controversy that results from including it in the final rule may detract from the public health benefits that will be realized from revising prescription drug labeling. The working group believes that devoting twenty-five pages of text to explaining and defending preemption in a rule revising content and format of labeling is conspicuous and peculiar.

We also question whether the specificity added to this version (which, we acknowledge, is an improvement), may have the unintended consequence of burdening FDA reviewers with additional labeling supplements or lengthy adverse reaction lists in proposed labeling in an attempt by applicants to meet the preemption principles outlined in the final rule at a time when we are striving to make the Adverse Reactions section of labeling more informative by including only those reactions necessary to characterize the safety profile of the drug.

Finally, we question whether FDA will be burdened by additional involvement with litigation. Irrespective of whether labeling negotiations are conducted with a complete paper record and whether there would be pressure to increase record keeping - something we would not welcome - there may be a significant increase in the number of requests to depose and interview FDA reviewers about preemption-related litigation and a similar increase in document requests.

Recommended changes

We have included in the attached redline version of Comment 13 a few revisions that are editorial in nature, either correcting inaccuracies or making the terminology consistent with the remainder of the preamble of the final rule. In addition:

- We believe the statement *"Preemption would include not only requirements imposed directly on manufacturers, but also requirements imposed on health care practitioners to disseminate risk information to patients beyond what is included in the labeling"* is unclear about which requirements are being referenced and who imposes these requirements (see proposed revision page 13, line 263).

- We believe that the phrase *"at least"* in the following sentence reduces clarity and may unintentionally broaden the intended scope of the preemption principles outlined in the final rule (see page 11, line 228): "With the adoption of this rule, FDA intends that in conjunction with existing preemption principles, at least the following claims be preempted by its regulation of prescription drug labeling...".

- Should the final rule clarify that the cited Dowhal v. SmithKline Beecham Consumer Healthcare case involved an OTC drug, and not a prescription drug?

We made no editorial changes to the Federalism section.