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VICE PRESIDENT
INTERNATIONAL AFFAIRS



January 11, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers lane, Rm. 1061
Rockville, MD 20852
<http://www.fda.gov/dockets/ecomments>

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Re: Docket No. 2005N-0479

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciate this opportunity to submit comments on the proposed March 2006 meeting of the World Health Organization's (WHO's) Expert Committee on Drug Dependence (ECDD). PhRMA is a voluntary, nonprofit organization representing the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for cures.

The ECDD makes recommendations for scheduling of substances under international conventions. WHO has announced a meeting of the ECDD for March 2006 and, as required by its own rules, has issued a call for data concerning use and abuse of substances that the ECDD will evaluate. These data are essential to good decision-making on the part of the experts. And, it is important to note, the decisions made by the ECDD have a powerful impact upon the availability of medicines in the United States and throughout the world. The problem: WHO has scheduled the meeting and issued the call for data on such short notice that the providers of the data cannot be expected to produce the information in time for the meeting. Also, WHO has improperly placed five substances on the meeting agenda for critical review.

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Pharmaceutical Research and Manufacturers of America

Timing

WHO announced the meeting in a communication dated October 27, 2005. Data are sought for nine substances. Because the ECDD meeting has been scheduled for March 28, 2006, WHO requires that the responses be made by January 3, 2006 in order that WHO can write the "critical reviews."

Pursuant to U.S. law, FDA has put a notice in the Federal Register dated December 13, 2005, calling upon interested parties to provide information in response to the WHO questionnaire. Attachment 1. These comments will be used by HHS to prepare the scientific and medical evaluation that will be forwarded to WHO. The responses are due thirty days after December 13: through the holiday season to January 12, 2006. The holidays will affect the ability of most pharmaceutical companies in the U.S. and Europe to respond. (Observe that the response date for the Federal Register notice is nine days after the time that WHO has requested a response from member countries.) Interested parties and HHS cannot be expected to do a proper job of data gathering and analysis in the time allowed.

We are aware that the reason for this unseemly rush is that funding for the ECDD meeting will expire at the end of March 2006. ECDD meetings are supposed to be held every two years; the last meeting was in 2002, over three years ago. The delay had no substantive rationale but was due entirely to internal organizational failings. Because WHO management tolerated this, the prescribed time for the biennial meeting is long past and now there is a race to have the meeting, driven by the desire to use the available funding.

WHO has been delegated the important role of evaluating the need to schedule substances under the international conventions to which most nations of the world are signatories. The ECDD provides WHO with the expertise to make those evaluations. ECDD recommendations will affect the availability of medicines. So there can be no doubt that the highest priority should be given to providing the expert committee with data that are carefully gathered and developed for their use.

WHO should be made to explain why it has mismanaged the ECDD meetings in such a manner that meetings were not held when they should have been. WHO should also be made to explain why having a meeting in March 2006

should be given priority over having a meeting at a time when the data can be provided in an orderly manner consistent with the gravity of the committee's task.

Substance

Senators Hatch, Biden and Levin have questioned WHO's action. *See* the senators' letter, Attachment 2. The executive branch of our government also has raised questions about the way the agenda for the March 2006 meeting has been put together; specifically, certain items are inappropriately on the agenda for critical review. *See* letter of Dr. William Steiger, Attachment 3. WHO has responded to Dr. Steiger's letter. *See* letter of Dr. Vladimir Lepakhin, Attachment 4.

The Executive Board of the World Health Assembly has prescribed certain rules for WHO to apply when conducting ECDD meetings; these rules appear in a document entitled *Guidelines for the WHO review of dependence-producing psychoactive substances for international control (Guidelines)*. Attachment 5. In its haste to call a meeting to save the funding, WHO has disregarded those rules, though in the response to Dr. Steiger, agency personnel say they have followed them.

The WHO response to Dr. Steiger misstates the circumstances in which the March 2006 ECDD has been called, and shows a lack of understanding of the *Guidelines* that are supposed to govern the operation of the ECDD. Certain substances are on the agenda when they clearly should not be. The WHO's explanations for having buprenorphine, tramadol, gamma-hydroxybutyric acid and oripavine on the agenda are specious.

WHO says buprenorphine is "... on the agenda, not for review, but because the Committee [meaning the 2002 ECDD] decided to make a final decision at the forthcoming ECDD." The *Guidelines* say nothing about "final decisions." The letter implies that the critical review of 2002 reached some kind of interim decision which should be honored by the subsequent ECDD as it makes a "final decision" that will finish the deliberations. But that is not what happened. The official report from the meeting shows that there was considerable confusion among the 2002 ECDD members concerning the criteria that should be used to classify buprenorphine. At the end of the meeting, the ECDD decided not to schedule buprenorphine. The ECDD report states: "For the reasons stated above, the Committee considered that the final decision on buprenorphine should be taken at a future meeting of the Committee." The plain meaning of that language is that the

2002 ECDD made no scheduling recommendation. Sentiments expressed during deliberations do not amount to a recommendation. Moreover, the idea that a future ECDD would render a “final decision” based on an out-dated analysis is bad policy that would result in very bad medicine.

The WHO letter does acknowledge that the 2006 ECDD should be governed by the *Guidelines* document, which clearly states the preconditions to be met for a critical review to occur:

Critical Review

15. Critical review is conducted by the Expert Committee in any of the following cases: (1) there has been notification from a Party to the 1961 or the 1971 Convention concerning the scheduling of a substance; (2) there has been an explicit request from CND to review a substance; (3) pre-review of a substance has resulted in a recommendation for critical review as indicated in paragraph 13 above; (4) information is brought to WHO's attention that a substance is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Member State. If therapeutic use of the substance is confirmed subsequently by any Member State in respect of case (4), the substance shall be subjected to a pre-review.

None of these preconditions has been met. After the critical review of the 2002 ECDD, in order to proceed to another critical review, it would be necessary to follow the procedures set forth in paragraph 13 of the *Guidelines*. There is no provision for ongoing critical reviews; that is, reviews that transfer from committee to committee until a desired result is obtained.

By calling the review of the 2006 ECDD a “final decision” WHO ignores the fact that the 2002 ECDD made no recommendation to reschedule the drug and, more problematic, ignores the mass of data that have been accumulated since 2002. WHO evinces no interest in the current data on buprenorphine. WHO's questionnaire only asks if moving buprenorphine to the Single Convention will affect medical availability. But how could the ECDD properly answer that question without some consideration of the medical use of the product, as would be adequately understood only if the current data were made available?

It is particularly disturbing that WHO is now acting to undercut the authority of the World Health Assembly, which is the governing body of the agency. The *Guidelines* are the rules approved by the Executive Board of the World Health Assembly, WHO's governing body. The 2002 ECDD asked that the *Guidelines* be clarified so that committees could have clearer criteria to determine whether to categorize a substance as a psychotropic or a narcotic. The committee asked for this additional guidance when considering buprenorphine and oripavine. Subsequently, WHO formed an ad hoc committee that drafted supplementary guidelines that attempted that clarification. However, the draft was not accepted by the Executive Board of the WHA when it met in January 2005. The Summary Records of that meeting state that the supplemental guidelines would not be accepted; WHO's Dr. Lepakhin, Assistant Director-General, is reported to have said "... the need for clarification remained. It would be worthwhile to continue working on the matter with a view to providing the Expert Committee with the guidance it had requested." The chairman suggested that the "... Secretariat and the Expert Committee on Drug Dependence ... continue their work on the issue."

Now, rather than following the current *Guidelines* or proposing supplementary guidelines, WHO is using its lawyers. The WHO response to HHS says, (concerning buprenorphine and oripavine) "for [these] substances, proposals for decisions which are mainly a legal matter now, are in preparation with involvement of WHO's legal department." Rather than clarify the *Guidelines*, which would require action by the Executive Committee, WHO proposes to let its lawyers advise and direct the next ECDD. This is a palpable effort to bypass the scrutiny of the Executive Board.

Tramadol, we are told, is up for review because "...the Committee recommended that the subject be placed on the agenda again." That is not true. The official report of the ECDD 2002 meeting states: "The information available is not sufficient for the Committee to recommend international control of tramadol, but is adequate to recommend that WHO keep the drug under surveillance."

The ECDD is not empowered to order on-going or serial critical reviews. To repeat, the preconditions for critical reviews are set forth in paragraph 15 of the WHO's *Guidelines* document. The rules for critical reviews simply do not allow the expert committees to hold over a drug for critical review meeting after meeting. The ECDD has previously followed the rules. For example, diazepam has been reviewed three times; each time getting a pre-review before the critical review. Another example is tramadol itself. Tramadol has been reviewed two times. It was pre-reviewed by the ECDD in 1992 when the committee decided not to subject

it to critical review. In 1998, the ECDD again decided to review tramadol and requested a pre-review as required under the guidelines. The 1998 ECDD recommended a critical review for tramadol. Buprenorphine was also subject to a pre-review and critical review when it was reviewed in 1988. In 2000 the ECDD conducted another pre-review of buprenorphine before it was subject to a critical review.

When the 2002 ECDD finished its report, its work was done and the critical review process was completed. The 2006 ECDD can only do a critical review when there has been a pre-review or one of the other three conditions stated in paragraph 15 of the *Guidelines* has been met, and none has been. It is therefore inappropriate for the WHO secretariat to place tramadol on the agenda for critical review.

The WHO's lack of understanding of the *Guidelines* is also revealed in the explanation for putting gamma-hydroxybutyric acid on the agenda: "... information has been brought to WHO's attention which justifies the issue to be put on the agenda." WHO does not cite one of the four reasons in paragraph 15, so the proper handling of gamma-hydroxybutyric acid would be to put it on the agenda for pre-review, in accordance with paragraph 13 of the *Guidelines*.

Dronabinol is also on the agenda, though in 2002 it was subjected to a critical review and a scheduling recommendation was made by that ECDD. Again, no explanation is provided to justify why, without a pre-review, this substance is again being subjected to a critical review. Rather, WHO in its response to Dr. Steiger says "... the Committee reported on it after its (2002) meeting, but ... the report was not sent out by WHO." The requirements of paragraph 15 are not mentioned, and not met.

Perhaps most extraordinary, WHO attempts further to justify its actions by stating the agenda is only a draft, and the final agenda will be decided by the ECDD at the start of the meeting. If this is true then there should be even greater concern about the manner in which WHO is carrying out its mandate under the conventions. Are the signatory nations gathering data for substances that will not be reviewed?

Conclusion

The ECDD is not being managed properly. This is proven by the missed meetings and procedures that do not follow the express rules given WHO by the Executive Board of the World Health Assembly.

PhRMA requests the following:

- 1) That FDA grant an additional thirty days within which to respond to this Federal Register notice;
- 2) That FDA request WHO to delay the ECDD meeting until such time that a proper presentation of medical and scientific information can be made; and
- 3) That FDA request WHO to remove the five substances – tramadol, buprenorphine, oripavine, dronabinol, and gamma-hydroxybutyric acid – that are inappropriately placed on the agenda of the March 2006 ECDD meeting.

Should WHO not accede to the foregoing changes, PhRMA requests that our government call this matter to the attention of the members of the Executive Board of the World Health Assembly. WHO's handling of this matter is a fit subject for consideration by the governing body of that agency.

Thank you for your consideration of these comments.

Sincerely,



Handwritten signature of Geralyn S. Ritter in cursive script.

Geralyn S. Ritter