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

Re: International Drug Scheduling; Convention on Psychotropic Substances; 4-Bromo-2,5-dimethoxyphenethylamine (2C-B); Gamma-hydroxybutyric acid (GHB); 4-Methylthioamphetamine (4-MTA); N-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MDBD); Diazepam (INN); Zolpidem (INN), 65 Fed. Reg. 24969 (April 28, 2000), FDA Docket No. 00N-1257.

To Whom It May Concern:

Hoffmann-La Roche Inc. (Roche) provides this response to the Federal Register announcement of April 28, 2000, requesting comments on the World Health Organization (WHO) communication on the international scheduling of certain drug products. 65 Fed. Reg. 24969.

Roche is a health care company that has been providing prescription medicines and other health care products in the United States and worldwide for over 100 years. Roche developed the class of drugs known as benzodiazepines in the mid-1950s. These drugs have become among the most widely used medications because of their high degree of efficacy, safety and tolerability in the treatment of anxiety, insomnia and other medical conditions. One of the benzodiazepines marketed by Roche is diazepam.

The Department of Health and Human Services (DHHS) Federal Register notice states that WHO is considering the international rescheduling of diazepam. International scheduling actions are profoundly important events, affecting medical practice and the

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availability of medicines. The people of the United States must live with the consequences of decisions made in these deliberations. The DHHS notice provides insufficient time for interested persons to submit meaningful comments. Also, due to the short timeframe for comments, the information requested by WHO is unlikely to solicit comprehensive scientific and medical information.

Given the short time that FDA has provided for public comment, Roche submits the following brief comments on the DHHS request for comments in response to the WHO proposed critical review of diazepam and other substances.

A. SUMMARY

- The current scientific and medical evidence demonstrate that diazepam is appropriately controlled in Schedule IV under the international convention and U.S. law.
- Rescheduling diazepam will send the wrong message to physicians and patients about the safety and efficacy of diazepam and will likely negatively affect prescribing practices and medical use.
- The WHO critical review process, including the current WHO questionnaire will not produce an evidence-based scientific and medical evaluation of diazepam and the other substances.
- The DHHS Federal Register notice provides insufficient time for meaningful public comment.
- DHHS and the U.S. government should take an active role prior to the Expert Committee on Drug Dependence meeting to ensure that the committee considers scientific and medical evidence on therapeutic use as well as considering well studied and documented patterns of abuse.

B. DIAZEPAM IS APPROPRIATELY CONTROLLED IN SCHEDULE IV

Diazepam is a safe and effective medicine similar to other benzodiazepines. Benzodiazepines play an essential role in modern clinical practice, not only in the treatment of sleep disorders but in a wide variety of psychiatric and medical uses. Benzodiazepines, including diazepam, used in the treatment of sleep and anxiety disorders share a common basic mechanism of action although they differ in certain pharmacologic characteristics. WHO has recognized the cost to society of insomnia and anxiety and the need to treat these medical conditions effectively and has therefore designated diazepam as an Essential Drug. As an Essential Drug, diazepam should be readily available at all times and in adequate amounts in hospital settings.

Evaluation of the scientific and medical data on diazepam does not support rescheduling of the drug under international treaties. WHO has reviewed diazepam at least five times since the drug was approved for use in the 1970s. The most recent critical review of diazepam, in 1990, found that the available pre-clinical and clinical data did not provide a basis for differentiating diazepam from the other benzodiazepines. DMP/PND/90.3 Annex 12. This critical review also stated that there were no epidemiological data regarding diazepam abuse that suggested significant non-medical use of benzodiazepines generally or diazepam relative to other benzodiazepines. The data have not changed; in the last ten years there have been no new data to suggest that diazepam is not being appropriately controlled in Schedule IV.

Diazepam is a frequently prescribed drug in the United States. However, misuse of diazepam, relative to its prescribing, is low. Recent estimates of seizures of diazepam by federal and state authorities indicate that seizures represent less than one percent of all prescriptions for diazepam. In addition, in the latest semiannual Drug Abuse Warning Network (DAWN) report for 1999 diazepam represented only 1.1% of all emergency room mentions. Between 1993 – 1999 DAWN mentions of diazepam were relatively constant and did not increase.

There is evidence of diazepam abuse primarily among individuals predisposed to drug abuse. However, the scientific and medical evidence does not demonstrate that diazepam's potential for abuse is significantly different than other benzodiazepines. The hearing on benzodiazepines and related substances conducted by FDA on September 11, 1997 provides further support that diazepam is appropriately controlled in Schedule IV. FDA, Public Hearing, Benzodiazepines and Related Substances (Sept. 11, 1997). The hearing brought together a number of authoritative experts on the role of these medications in clinical practice, as well as on pre-clinical, clinical and epidemiological evidence of their liability for abuse. The experts agreed that benzodiazepines have come to play an essential role in modern clinical practice, not only in the treatment of sleep and anxiety disorders but in a wide variety of psychiatric and medical uses. One of the reasons that benzodiazepines have been adopted so extensively and in so many medical uses is undoubtedly their safety. Benzodiazepines are "infinitely safer" than the

barbiturates, the previous generation of sedative-hypnotics. Testimony of Thomas Wyatt former Executive Director, National Association of Controlled Substances Authority, at 156 (FDA, Public Hearing, Benzodiazepines and Related Substances (Sept. 11, 1997)).

Several experts provided testimony that benzodiazepines, including diazepam, have a low liability for abuse. Dr. James Woods of the University of Michigan concluded that “benzodiazepines have a very low liability for abuse among the general population or among the people for whom they are typically prescribed.” Testimony of James Woods at 177. Similarly, Dr. John Roache of Johns Hopkins, who opined that there are some differences in abuse potential among benzodiazepines, stated that overall “there’s a very low potential for abuse in most therapeutic users.” Testimony of John Roache at 72.

Rescheduling diazepam or other benzodiazepines would have no useful effect on reducing benzodiazepine abuse, but would adversely affect appropriate medical use of these drugs. A number of participants at the FDA hearing expressed the view that current controls on benzodiazepines, including diazepam, are appropriate. Dr. David Greenblatt of Tufts University stated that the core understanding of benzodiazepine treatment has not changed substantially over the last 10 years, and that there is no new finding or new revelation requiring immediate action. Testimony of David Greenblatt at 105-6. He also

stated that he thought that the current controls on benzodiazepines are acceptable. Id. at

108. Dr. Woods commented that

[i]t is worth noting that, in the United States, benzodiazepines as a group have historically been subject to relatively lenient restrictions; that is, Schedule IV of the CSA.... It is also worth noting that this level of control appears generally appropriate; that is, despite some alarms that were raised in the early 1970s about a growing epidemic of abuse of these drugs, history hasn't borne out this concern. There is no evidence of anything like an epidemic of such abuse in this country or any other. Indeed,... there is virtually no abuse of benzodiazepines in the general population.

Testimony of James Woods at 180-81. Dr. David Smith of Haight Ashbury Free Clinics expressed a similar view "that the vast majority of benzodiazepines used in United States are used for appropriate therapeutic purposes." Testimony of David Smith at 253.

Dr. Woods stated that increasing restrictions on the prescription and availability of drugs for the treatment of anxiety and insomnia would be likely to exacerbate the problem of undertreatment of the millions of people who suffer from these disorders. Testimony of James Woods at 175-76. The danger is that increasing restrictions on benzodiazepines would convey to physicians and patients the misleading message that these drugs carry a substantial risk of abuse and/or dependence. This message could deter physicians from prescribing the drugs and deter patients from taking them. As Dr. Woods noted in his presentation, the increased restriction imposed on benzodiazepines by the state of New York in 1989 resulted in prescriptions for the drug declining by about half the following year. Id. at 191. Dr. Woods noted some effects of this decrease in

prescriptions for benzodiazepines. Prescriptions for non-benzodiazepines, including meprobamate, barbiturates, and older sedative-hypnotics that the benzodiazepines had replaced because the benzodiazepines were more effective and less hazardous, increased, presumably because physicians substituted these other agents for benzodiazepines. Id. at 192. This increase in prescriptions for substitutes, however, did not offset the decrease in benzodiazepine prescriptions, suggesting that another result of the New York restriction might have been to increase the problem of undertreatment. Id.

Dr. James Ballenger, representing the American Psychiatric Association (APA), expressed concern that the public did not fully appreciate the safety and benefits of benzodiazepines. Dr. Ballenger stated:

[none of experts testifying] say that there is anything more than just a very small amount of abuse potential for the benzodiazepines in the traditionally anxious patient. It's overwhelmingly all in the polysubstance-abusing patient.

Testimony of James Ballenger at 243. Dr. Ballenger concluded that rescheduling any benzodiazepine would have a serious effect on patient care:

[I]f you took [one, two, or three benzodiazepines] and moved it down to more regulation, into [schedule] III or II, the public would conclude . . . I knew all along these were very, very dangerous drugs.... The public is prepared to believe the worst about these drugs.

Id. at 246-47. Dr. Ballenger's point was that the public has been misinformed about benzodiazepines and more education is needed about the safety and efficacy of these drugs.

In summary, based on the scientific, medical or epidemiological data indicating that diazepam has only a low abuse potential, diazepam should not be rescheduled under international schedules.

C. WHO CRITICAL REVIEW PROCESS

The 1971 Convention on Psychotropic Substances (“1971 Convention”) and other treaties, such as the 1961 Convention on Narcotic Drugs (the “1961 Convention”) and the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (the “1988 Convention”), establish the system of international controls for substances of abuse. This system has been supported by most of the international community for the past forty years. The DHHS Federal Register notice brings attention to the manner in which the scheduling responsibility is executed by WHO; the process used by WHO will not lead to development of evidence-based medical and scientific recommendations on diazepam and other drugs under review.

Every two years WHO convenes an Expert Committee on Drug Dependence (ECDD). The ECDD is an expert advisory committee established to “carry out a medical and scientific evaluation of abuse liability of dependence-producing drugs” and to make recommendations to the U.N. Commission on Narcotic Drugs (CND) on international control of these substances. The ECDD’s recommendation will be used by WHO’s Director General, who will communicate her recommendations to the CND. The CND will consider whether to schedule the substances. It is a fact that, in the past, the CND has accepted “almost all” of WHO’s scheduling decisions. ECDD Thirty-first Report, WHO Technical Report Series 887, at 1 (Geneva 1999) (the “Thirty-first Report”). Also, the WHO recommendations are binding as to medical and scientific matters. See 1971 Convention art. 2, para. 5.

Under the pre-existing ECDD guidelines, and the more general WHO advisory committee regulations, only the member states and nongovernmental organizations (NGOs) have any standing to actively participate in the process. Participation in the international scheduling process is limited to governments, NGOs, national health authorities and affiliated organizations such as ICPO/Interpol. Industry and other interested persons are unable to actively participate in the scheduling recommendations.

The recent critical review of ephedrine illustrates the problems with the current process and the need to improve WHO's review of the relevant scientific and medical information. In 1998, WHO recommended that some isomers of ephedrine be placed in Schedule IV of the 1971 Convention. However, WHO's recommendation did not take into account the interaction between the 1971 and 1988 Conventions, and failed to document the scientific basis for the recommendation in a coherent manner. Specifically, the "abuse" cited was limited to anecdotal information about abuse "in certain African countries" and also of abuse of ephedrine in dietary supplements. 64 Fed. Reg. 1629, 1630 (Jan. 11, 1999) (reprinting the WHO recommendation). Also, interested parties within the United States were hampered by FDA's failure to make important information about the international scheduling of ephedrine available in a timely manner. In the case of ephedrine, FDA did not publicize the WHO questionnaire until more than two weeks after the response was to be submitted. See 63 Fed. Reg. 13258 (Mar. 18, 1998). Further, the agency's response to ephedrine questionnaire was not revealed to the public until more than six months after the ECDD meeting. See Isomers of Psychotropic Substances; Three Drug Substances, FDA Docket No. 98N-0148, <<http://www.fda.gov/ohrms/dockets/dockets/98n0148/2.htm>> (noting that FDA's response was added to the docket on February 2, 1999).

In recognition of the jurisdictional problem and the lack of a scientific basis for its scheduling recommendation, the CND referred the matter back to WHO for further review. There has been no further action on this substance.

In the case of ephedrine, WHO's reliance on anecdotal abuse information may have been caused, at least in part, by the agency's use of an inadequate questionnaire. See 63 Fed. Reg. at 13258 (reprinting the ECDD questionnaire). The present questionnaires are similar in methodology to those used for ephedrine. As we describe in detail in Section D below, the present questionnaires invite the member states and other recipients to respond with anecdotal information instead of evidence-based scientific information necessary for an analysis and subsequent decision making as required by the 1971 Convention.

The need for process reform becomes all the more evident as the scheduling decisions are made with increasing numbers of substances, and in situations where there may not be universal agreement concerning the data or the implications of the data. Only by refining the process, allowing all interested parties to participate, and by encouraging rigorous scientific analysis of data, will we assure that the Convention system is successful.

D. THE CURRENT CRITICAL REVIEW

In the ECDD's Thirty-first Report, the committee recommended that six substances be considered for critical review to determine whether certain scheduling actions are necessary under the 1971 Convention. Thirty-first Report at 11-18. In September 2000, the ECDD will meet again to consider whether to recommend that the subject products be controlled and, if so, in what schedule as defined by the Convention. In anticipation of the ECDD meeting, WHO on January 12, 2000 sent questionnaires to

member states and other NGOs recognized by the agency. The questionnaires are revealed to interested parties for comment in the Federal Register notice.

1. The Who Questionnaires Should be Revised

The Federal Register cites the WHO statement that “[o]ne of the essential elements of the established review procedure is for [WHO] to collect relevant information from Member States to prepare a Critical Review document for submission to the Expert Committee on Drug Dependence.” 65 Fed. Reg. at 24969. The Federal Register announcement does not quote the text or style of the questionnaires sent to the United States and other member states. Rather, the announcement sets forth the following:

WHO Questionnaire for review of dependence-producing psychoactive substances by the Thirty-second Expert Committee on Drug Dependence.

Substance reported on:

- 1. Availability of the substance (registered, marketed, dispensed, etc.);*
- 2. Extent of the abuse or misuse¹ of the substance;*
- 3. Degree of seriousness of the public health and social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.); and*
- 4. Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.).*

¹ In this questionnaire, “abuse or misuse” refers to use of the substance other than for medical or scientific purposes.

In addition to the above, with regard to Diazepam (INN) report on:

5. The impact of transferring diazepam from Schedule IV to Schedule III of the Convention on Psychotropic Substances, 1971, and its effect on availability for medical use.

In addition to items 1 to 4 above, with regard to Zolpidem (INN) report on:

6. The impact of placing zolpidem in Schedule IV of the Convention on Psychotropic Substances, 1971, and its effect on availability for medical use.

Id. at 24970.

International scheduling recommendations are public health policy determinations that require independent, objective information on the magnitude of any threat to public health and worldwide health trends. To reach an understandable, useful result, an evidence-based inquiry into a public health issue such as substance abuse requires standard units of measure, comparable data-collection methods and rigorous analysis to achieve a meaningful recommendation. The WHO questionnaires and revised Federal Register questions simply do not elicit meaningful information that will serve as the foundation of a potential recommendation which could have a substantial impact on medical practice and patient care.

2. The WHO Questionnaires Do Not Elicit Information that is Necessary for Evidence-Based Scheduling Determinations

The WHO questionnaires seek information on six substances: (1) 4-bromo-2,5-dimethoxyphenethylamine (2C-B); (2) gamma-hydroxybutyric acid (GHB); (3) 4-methylthioamphetamine (4-MTA); (4) N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB); (5) diazepam; and (6) zolpidem. The questionnaires for 2C-B, GHB, 4-MTA, and MBDB are identical despite different pharmacological properties,

indications for legitimate use and scenarios for abuse potential. Each questionnaire asks only three questions: (1) whether there is any legitimate use of the substance, including medical uses in the member country; (2) whether the substance is “abused or misused” in the member country; and (3) whether there are any related illicit activities in the member country.

The WHO’s diazepam and zolpidem questionnaires vary slightly from the others, presumably because diazepam and zolpidem are known to have some legitimate therapeutic uses. Evidently for this reason the questionnaire asks about the substances’ marketing status – a question that will not elicit proper detail about the therapeutic usefulness of the substance in the member states. The diazepam and zolpidem questionnaires also add a fourth question to inquire as to whether an international scheduling decision would affect the substances’ medical availability, without inquiring about whether the product is medically available and to what degree it is available. These questionnaires also minimize the impact on patient and physician perception of what international scheduling means.

None of the WHO questionnaires makes inquiries that will result in the collection of scientific evidence; rather, they elicit/encourage the submission of unsubstantiated information. Many of the questions are designed for yes or no answers, for example: “Is the substance abused or misused in your country (Yes/No).” Additional information about the extent of the abuse is to be provided in the three lines that follow. That additional information is likely to be totally undirected, limiting its use for evidence-based judgments.

The current questionnaires are biased against making an accurate assessment of the substances’ potential for therapeutic use. The WHO questionnaires also do not request detailed information on the importance of the therapeutic uses, or the magnitude of the health problems associated with the alleged misuse of these medicines. The lack of

such specific information will make it difficult to assess any worldwide therapeutic use trends or possible health problems. Any report based on the answers received can only be a description of anecdotal information and does not provide a meaningful basis for statistical analysis. The questionnaires provide no way of discerning whether a reported problem is an isolated occurrence or an ongoing epidemic. Further, the questionnaires do not seek information about the availability of therapeutic alternatives – a vital factor that is likely to vary widely from country to country.

3. The WHO Questionnaires Do Not Elicit Information That Is Required By The 1971 Convention

The 1971 Convention is very specific with respect to the criteria for international scheduling. Under the Convention, WHO may recommend a substance for international scheduling only upon finding:

(a) That the substance has the capacity to produce

(i)(1) A state of dependence, and (2) central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking or perception or mood, or

(ii) Similar abuse and similar ill effects as a substance in Schedule I, II, III, or IV, and

(b) That there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

1971 Convention art. 2, para. 4 (emphasis added).

In addition, the 1971 Convention requires WHO to communicate three findings to the CND: (1) “the extent or likelihood of abuse,” (2) “the degree of seriousness of the public health and social problem,” and (3) “the degree of usefulness of the substance in medical therapy....” Id.

The official commentary to the 1971 Convention (the “1971 Convention Commentary”) makes clear that a substance warrants international control only if the degree of risk to public health and associated social problems outweigh the usefulness of the drug in medical therapy. See 1971 Convention Commentary art. 2, para. 4, cmt. 44. The risk balance is to be evaluated according to the following scale:

Schedule	Degree of Seriousness of the Public Health or Social Problem	Therapeutic Usefulness
I	Especially Serious	Very Limited, If Any
II	Substantial	Little to Moderate
III	Substantial	Moderate to Great
IV	Smaller, But Still Significant	Little to Great

Id. cmt. 50.

The 1971 Convention Commentary stresses that the degree of therapeutic usefulness is “very important . . . in choosing the particular [scheduling] regime....” Id. cmt. 44. Moreover, the 1971 Convention Commentary notes that “[i]t is apparent that in determining the usefulness of a medicine not only its potential beneficial effects, its value in the case of grave medical indications and the extent and frequency of its employment but also the intensity of its dangerous properties . . . may have to be taken into account.” Id.

The questionnaires do not address the critical issue – the degree of therapeutic usefulness. See 1971 Convention art. 2, para. 4. The “legitimate use” questions also fail to assess the substances’ “value in the case of grave medical indications” and “the extent and frequency of . . . employment....” 1971 Convention Commentary art. 2, para. 4, cmt. 44. Without this basic information, the ECDD lacks the data required to render a determination of the substance’s therapeutic usefulness. To illustrate the significance of this omission, the questionnaire for diazepam would not garner the information that this medicine is designated as an Essential Drug because, among other reasons, it can be used effectively to treat seizures in countries where there are no other easily available means to treat them.² The member states should be guided by the questionnaires to provide their information concerning the degree of usefulness of medicines in their countries.

4. Scheduling Decisions Should be Made with Due Care
Particularly for Essential Drugs

It is not “too late” to issue proper questionnaires. Time is not the issue with the scheduling process. The idea that the Convention system should be compromised “this time” in order to avoid re-starting or revising the ongoing process is simply unthinkable and is an injustice to the physicians and patients and the integrity of WHO. One of the drugs that will be affected by this process, diazepam, is an Essential Drug, and it is totally unacceptable that a drug that WHO has deemed so vital to the needs of the world should be accorded such cavalier treatment. The need to hastily proceed is not paramount over the need to produce a medically and scientifically justified work product. For the same reasons, an argument that many of the member countries will not answer the questionnaires if WHO requests more detail, is not acceptable – collection of data that are

² Diazepam has been identified as an “Essential Drug” by the WHO Expert Committee on the Use of Essential Drugs. See WHO Technical Report Series No. 882, at 29 (1998).

not useful is a violation of basic scientific principle and could result in a meaningless recommendation.

E. THE U.S. GOVERNMENT MUST ENSURE THAT THE WHO CRITICAL REVIEW IS EVIDENCE-BASED

The fact that WHO and the ECDD have lead roles in this process does not in the least diminish the responsibility of the U.S. government to take every measure necessary to assure that scheduling is accomplished in a manner that is based on the best scientific and medical evidence. The U.S. government and others will not be able to support the Convention system if WHO is unwilling or unable to administer a process that will lead to defensible scientific and medical judgments. The role of WHO is essential in the international drug control system. The U.S. government should request further study and evaluation of the WHO process.

Development of responses to WHO's request for scheduling-related information engages elements of the Departments of State, Justice, and Health and Human Services. The number of interested agencies contributes to the complexity of this task. Notwithstanding the inherent problems caused by having multiple responsible parties, the nongovernmental interests in the U.S. response are strong, and care should be taken to engage those interests in a meaningful way. The Federal Register notice provides interested persons with only 17 days from the date of publication to submit comments. The U.S. government should develop mechanisms to assure that important information about international scheduling actions is made public in time for meaningful comment. Specifically, the U.S. government should make a draft of its response available to the public for comment at least 30 days prior to forwarding it to WHO.

Finally, the DHHS should not defer commenting on its position in regard to scheduling until after the ECDD meeting. Because the CND almost always accepts the WHO scheduling recommendation, waiting until WHO submits its recommendation to

the CND will effectively negate the U.S. recommendation. There is no reason that the U.S. should not actively participate in the ECDD process by providing all relevant scientific and medical information to the committee, including the basis for its scheduling recommendation.

CONCLUSION

Scheduling actions are important and deserve adequate process, analysis and appropriate communication of findings due to their meaningful consequences for physicians and patients.

For the reasons stated above, the U.S. government should:

- (through DHHS) recommend that diazepam is appropriately controlled in Schedule IV under the international conventions and that the scientific and medical data available to DHHS and available to the agency support this position;
- request that WHO amend the questionnaires to solicit information on the nature, degree and scope of therapeutic use and quantification of abuse;
- actively participate in working with WHO and the UN to review and revise the procedures for conducting a critical review and recommending scheduling changes;
- revise the process by which DHHS provides notice to the public on the ECDD process to ensure sufficient opportunity for comment and participation in the process; and

- provide a scheduling recommendation before the ECDD meets so that this information can be considered by the ECDD.

Sincerely,

A handwritten signature in black ink, appearing to read "Dolly A. Judge". The signature is fluid and cursive, with a large initial "D" and "J".

Dolly A. Judge

Vice President

Hoffmann-La Roche Inc.